Original Article

Incident Asthma, Asthma Exacerbations, and Asthma-Related Hospitalizations in Patients With Atopic Dermatitis

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What is already known about this topic? Atopic dermatitis (AD) is thought to predispose to asthma development via the atopic march, and birth cohort studies to date have supported this notion, finding a higher incidence of asthma in children with AD.

What does this article add to our knowledge? Studies of AD and asthma that account for the impact of AD severity and the severity of asthma outcomes are limited. Our study further characterizes asthma risk related to AD in both children and adults.

How does this study impact current management guidelines? Risk of asthma and subsequent asthma-related exacerbation and hospitalization increase with the presence and severity of AD, especially in children. Those with more severe AD may benefit from increased attention to control of their asthma.

BACKGROUND: Atopic dermatitis (AD) is thought to induce asthma via the "atopic march," but the effects of AD on incident asthma and asthma severity have not been fully characterized.
OBJECTIVE: To determine risk of asthma, asthma exacerbations, and asthma-related hospitalizations among patients fwith AD.
METHODS: A cohort study was conducted using electronic health records data from UK general practices from 1994 to 2015. Children (<18 years old) and adults (≥18 years) with AD were matched on age, practice, and index date to patients without AD. AD severity was categorized using treatments and dermatologist referrals. Outcomes were incident asthma among

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Abbreviations used
AD- atopic dermatitis
BMI- body mass index
GP- general practitioner
HR- hazard ratio
IQR- interquartile range
THIN- The Health Improvement Network

all patients and asthma exacerbation or hospitalization among patients with asthma.
RESULTS: On comparing 409,341 children with AD (93.2% mild, 5.5% moderate, 1.3% severe) with 1,809,029 unaffected children, those with AD were found to be associated with a 2-fold greater risk of asthma compared with those without AD (hazard ratio, 1.96; 95% CI, 1.93-1.98). On comparing 625,083 adults with AD (65.7% mild, 31.4% moderate, and 2.9% severe) with 2,678,888 unaffected adults, AD was found to be associated with a 38% higher risk of asthma (hazard ratio, 1.38; 95% CI, 1.36-1.40). Asthmatic patients with AD also had a 21% to 63% greater risk of asthma exacerbations and a 20% to 64% greater risk of asthma-related hospitalizations compared with asthmatic patients without AD. Risk of asthma, asthma exacerbation, or asthma-related hospitalization increased with AD severity in a dose-dependent manner in both the pediatric and adult cohorts.
CONCLUSIONS: AD, especially in children and when more severe, is associated with greater risk of asthma as well as greater risk of asthma exacerbations and hospitalizations among asthmatic patients.

Key words: *Asthma; Atopic dermatitis; Atopy; Eczema; Epidemiology*

INTRODUCTION

Atopic dermatitis (AD) affects about 10% of adults and 20% of children and is associated with other allergic disorders including asthma.[1,2] The concept of the "atopic march" describes a progression from AD early in life to the subsequent development of other atopic conditions such as allergic rhinitis and asthma.[3] Several mechanisms may drive asthma development among patients with AD. In the classic paradigm of the atopic march, allergic sensitization of the skin occurs in the setting of barrier defects and immune dysregulation in AD-affected skin, leading to allergic sensitization in the airways, resulting in asthma. However, predisposition to both AD and asthma is likely driven by shared genetic and/or environmental factors; genome-wide association studies have identified many shared loci between AD and asthma, including variants in epidermal barrier and T_H2 immune response genes.[4,5]

An estimated 40% of patients with AD subsequently develop asthma.[3,6] However, most studies evaluating asthma risk among patients with AD have been conducted in birth cohorts of pre-adolescent children younger than 3 to 11 years.[7-13] One systematic review estimated a pooled odds ratio of 2.14 for asthma prevalence in children with AD who were younger than 4 years.[7] Asthma risk may also depend on AD disease characteristics, with specific phenotypes of AD before age 6 years having been found to be more associated with developing asthma.[9] In addition, although some observational studies suggest that more severe AD portends more severe asthma in children,[14] the effects of AD and AD severity on the severity of asthma have not been thoroughly characterized.

Less is known about asthma risk among older children and adults with AD. Increasing evidence suggests that adult-onset asthma may relate more to environmental exposures and comorbidities such as obesity compared with childhood-onset asthma.[15-18] Certain asthma subtypes may also be more highly associated with either pediatric or adult AD.[19] Previous studies examining the association of AD early in life with asthma later in life have primarily relied on surveys taken at specific time points.[20,21] One such study found that childhood AD was associated with incident asthma in adolescence (hazard ratio [HR], 2.14) and adult life (HR, 1.63).[21]

In this study, we use electronic health records data to further characterize the incidence of asthma, including risk of asthma exacerbations and hospitalizations, among both children and adults with AD in a population-based cohort.

METHODS

We conducted a cohort study using The Health Improvement Network (THIN), an electronic medical records database of more than 600 general practices in the United Kingdom that is broadly representative of the UK population. The general practitioner (GP) is the primary contact for medical care in the United Kingdom, and diagnostic codes for many conditions, including AD, have been validated in THIN.[22,23] Because 96% of patients with AD are managed exclusively by GPs, a primary care database such as THIN is generalizable to the greater population of patients with AD.[24] Data collected between 1994 and February 2015 were used.

The study population included all patients with AD, each matched to up to 5 patients without AD (non-AD) on age (±3 years), general practice, and an encounter within ±6 months of the index date for the patient with AD (defined as latter of registration and diagnosis dates). Patients younger than 18 years and those 18 years or older were analyzed separately as pediatric and adult cohorts, respectively. Patients with AD were identified using a validated algorithm requiring at least 1 of 5 common diagnosis codes for AD *and* 2 AD-related therapy codes, which carries a positive predictive value of 90% (83%-96%) and 82% (73%-89%) for physician-confirmed AD diagnosis among children and adults, respectively.[22] Each patient without AD was assigned a "diagnosis date" on the basis of an encounter within ±6 months of the index date for the matched patient with AD to minimize bias by ensuring that AD and non-AD groups were followed during similar time periods. Follow-up time for patients with AD began at the latest of AD diagnosis, practice registration, or Vision date (ie, when the Vision software was implemented for data transfer, thereby ensuring good data quality). For patients without AD, follow-up time began at the latest of the diagnosis date, registration date, or Vision date. Follow-up ended at the earliest of asthma development, transfer out of the practice, death, or end of study period. Patients with a history of asthma at the time of cohort entry were excluded from the analysis of incident asthma.

We also identified a subcohort of asthmatic patients to evaluate the risk of asthma exacerbation and asthma-related hospitalization with respect to AD and AD severity. This subcohort included all patients with and without AD with a diagnosis of asthma at any time before or after entry into the larger cohort. Within this subcohort, follow-up

time began at the latter of the original start date, as defined earlier, and the date of first asthma code. Follow-up ended at the earliest of incident asthma exacerbation event, transfer out of the practice, death, or end of study period. Patients with history of asthma exacerbation events at start of follow-up were excluded from the analysis.

AD severity was defined as a time-updated variable using treatments as proxies. All patients with AD were considered to have mild disease by default. They were classified as having "moderate" AD at the first of (1) a second potent topical corticosteroid treatment within 1 year or (2) a first topical calcineurin inhibitor treatment (which is reserved for moderate AD in the United Kingdom).[25] Patients were classified as having "severe" AD at the first of (1) systemic immunosuppressant treatment, (2) phototherapy use, or (3) referral to dermatology (because 96% of patients with AD are managed exclusively by GPs).[24] Once defined as having moderate AD, patients remained as such unless they developed severe AD; once defined as having severe AD, patients remained as such for the remainder of the follow-up. Therefore, patients belonged to 1 of 3 severity categories at any given time. Although not directly validated, this time-updated approach to defining AD severity has been previously used.[26,27]

The primary outcomes were (1) incident asthma across the overall cohort, (2) incident asthma exacerbation events, and (3) asthma hospitalization events within the subcohort of asthmatic patients. We identified outcomes using READ diagnosis codes, which make up a comprehensive numerical system analogous to the *International Classification of Diseases* codes used to record diagnoses in THIN.[28] Incident asthma was identified by having a READ diagnosis code for asthma in a patient with no previous history of an asthma diagnosis code. Asthma exacerbation was identified using READ diagnosis codes for asthma exacerbation in a patient with a history of asthma. Asthma-related hospitalizations were defined as having a hospitalization within 14 days of an asthma READ diagnosis code.

Incidence rates were calculated for each outcome. Cox regression models were used to compare time-to-incident outcomes, adjusted for covariates determined *a priori:* age, sex, socioeconomic status (ie, Townsend index, a measure of material deprivation), and history of allergic rhinitis. Body mass index (BMI),[16,29] smoking status,[30,31] and alcohol intake[32] were also adjusted for in adult models; missing data prevented these variables from being included in pediatric models. Covariates were defined at time of cohort entry; AD severity and age were time-updated. We did not include *P* values to compare baseline characteristics between study groups, because small absolute differences may be statistically significant in the context of our large sample size but do not necessarily equate to clinically significant differences. We conducted several sensitivity analyses to address possible sources of bias. To address potential outcome misclassification, we used an alternative definition of asthma exacerbation to reflect an asthma diagnosis code with a systemic corticosteroid prescription within 3 days. To address short study follow-up duration, a sensitivity analysis restricted to patients with at least 5 years of follow-up was conducted. To address ascertainment bias, we also included another analysis restricted to patients seen at least yearly during follow-up. Sensitivity analyses restricting to childhood-onset asthma outcomes and stratifying by early and late childhood in the pediatric cohort were also conducted.

RESULTS

Pediatric cohort

A total of 409,431 children with AD (93.2% mild, 5.5% moderate, and 1.3% severe) were matched to 1,809,029 children without AD. The median age was 4 (interquartile range [IQR], 1-8), 9 (IQR, 4-14), 5 (IQR, 1-10), and 4 (IQR, 2-9) years for the mild, moderate, severe, and non-AD groups, respectively. Socioeconomic status was not meaningfully different between the AD and non-AD groups. Median follow-up duration was between 5 and 7 years (Table I), and 18% of patients in the pediatric cohort had follow-up beyond age 18 years. The subcohort of asthmatic patients consisted of 169,679 patients without AD (9.4% of the total non-AD pediatric cohort) and 57,098 patients with AD (13.9% of the total AD pediatric cohort). Compared with the overall cohort, the asthmatic subcohort was older (median age, 9-12 years) and had longer follow-up time (7-10 years) (Table II).

Incidence rates of asthma, asthma exacerbations, and asthma hospitalizations among children were higher in the presence of AD and increased with greater AD severity (Table III). Of all incident asthma cases, 96% occurred before age 18 years. Adjusted for age, sex, socioeconomic status, and history of allergic rhinitis, the risk of new-onset asthma was about 2-fold greater among children with AD compared with those without AD (HR, 1.96; 95% CI, 1.93-1.98) (Figure 1). When stratified by AD disease severity, there was a dose-response relationship whereby more severe AD was associated with an increasingly higher risk of asthma (mild AD: HR, 1.82 [95% CI, 1.80-1.85]; moderate AD: 3.24 [95% CI, 3.13-3.35]; severe AD: 3.70 [95% CI, 3.50-3.92]). Among children with asthma, the risk of incident asthma exacerbation was 63% higher overall among those with AD versus those without AD (HR, 1.63; 95% CI, 1.59-1.68), with the greatest risk among children with moderate or severe AD (HR, 2.33 [95% CI, 2.21-2.47] and 2.69 [95% CI, 2.45-2.95], respectively) (Figure 1). Relative to children without AD, the risk of asthma-related hospitalization was 64% higher among all children with AD but 163% to 195% higher among those with moderate or severe AD (Figure 1). Overall, 3862 excess asthma exacerbations and 1381 excess asthma hospitalizations were attributable to AD.

For all outcomes, sensitivity analyses restricted to patients seen at least annually during follow-up resulted in only slight attenuation of the effects observed in the primary analyses (Table IV). Similarly, sensitivity analyses restricted to patients with at least 5 years of follow-up or with at least 1 year of data before cohort entry resulted in nearly identical findings as the primary analyses. When asthma exacerbation was alternatively defined by the presence of an asthma diagnosis code with a systemic corticosteroid prescription within 3 days, the results also remained similar (Table IV). To distinguish adult-onset and pediatric-onset outcomes, we also included a sensitivity analysis restricting to only those with outcome onset before age 18 years, which showed similar results as the primary analyses (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). An additional sensitivity analysis stratified by age younger than 4 years and 4 years and older showed findings similar to the main effects (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Adult cohort

A total of 625,083 adults with AD (65.7% mild, 31.4% moderate, and 2.9% severe) were matched to 2,678,888 adults without AD. The median age was 47 (IQR, 32-64) years in the non-AD group and between 45 and 50 years in the AD groups, and there was a female predominance within all groups (Table I).

TABLE I. Baseline characteristics of pediatric and adult cohorts in THIN database, 1994 to 2015 (n = 5,522,431 patients)*

Characteristics	No AD	Mild AD	Moderate AD	Severe AD
Pediatric cohort	N = 1,809,029	N = 381,678	N = 22,433	N = 5,320
Age (y), median (IQR)	4 (2-9)	4 (1-8)	9 (4-14)	5 (1-10)
Sex, n (%)				
Female	872,279 (48.22)	184,682 (48.39)	11,054 (49.28)	2,335 (43.89)
Male	936,750 (51.78)	196,996 (51.61)	11,379 (50.72)	2,985 (56.11)
Townsend deprivation index, n (%)				
1: Lowest	424,409 (24.71)	89,820 (24.89)	4,768 (22.55)	1,251 (25.00)
2: Low	340,677 (19.84)	71,979 (19.95)	4,106 (19.42)	1,069 (21.37)
3: Moderate	355,559 (20.70)	75,261 (20.86)	4,551 (21.52)	1,033 (20.65)
4: High	339,336 (19.76)	70,649 (19.58)	4,316 (20.41)	900 (17.99)
5: Highest	257,540 (14.99)	53,113 (14.72)	3,407 (16.11)	750 (14.99)
Unknown	91,508 (5.06)	20,856 (5.46)	1,285 (5.73)	317 (5.96)
Person-time (y), median (IQR)	5.0 (2.0-9.4)	5.2 (2.1-9.7)	6.0 (2.6-10.2)	6.9 (2.7-12.6)
History of asthma, n (%)	169,679 (9.38)	49,782 (13.04)	6,094 (27.17)	1,222 (22.97)
History of allergic rhinitis, n (%)	75,050 (4.15)	23,935 (6.27)	2,870 (12.79)	521 (9.79)
Adult cohort	N = 2,678,888	N = 410,867	N = 196,101	N = 18,115
Age (y), median (IQR)	47 (32-64)	45 (30-63)	50 (34-68)	47 (32-63)
Sex, n (%)				
Female	1,445,589 (53.96)	256,071 (62.32)	109,404 (55.79)	10,736 (59.27)
Male	1,233,299 (46.04)	154,796 (37.68)	86,697 (44.21)	7,379 (40.73)
BMI (kg/m^2), n (%)				
Underweight (<18)	72,655 (2.71)	11,504 (2.80)	4,150 (2.12)	525 (2.90)
Normal (18.5-24.9)	911,449 (34.02)	152,480 (37.11)	66,015 (33.66)	6,972 (38.49)
Overweight (25-29.9)	707,292 (26.40)	109,693 (26.70)	56,021 (28.57)	4,799 (26.49)
Obese (30-34.9)	285,567 (10.66)	44,998 (10.95)	24,088 (12.28)	1,900 (10.49)
Severely obese (35-39.9)	94,373 (3.52)	15,720 (3.83)	8,486 (4.33)	653 (3.60)
Morbidly obese (>40)	44,721 (1.67)	8,341 (2.03)	4,525 (2.31)	343 (1.89)
Unknown	562,831 (21.01)	68,131 (16.58)	32,816 (16.73)	2,923 (16.14)
Smoking status, n (%)				
Never	1,293,811 (48.30)	206,577 (50.28)	89,588 (45.68)	8,653 (47.77)
Current	576,463 (21.52)	84,855 (20.65)	44,195 (22.54)	3,914 (21.61)
Former	548,828 (20.49)	92,290 (22.46)	48,636 (24.80)	4,182 (23.09)
Unknown	259,786 (9.70)	27,145 (6.61)	13,682 (6.98)	1,366 (7.54)
Drinking status, n (%)				
Never	300,614 (11.22)	51,208 (12.46)	24,278 (12.38)	2,338 (12.91)
Current	1,655,958 (61.82)	262,008 (63.77)	125,921 (64.21)	11,525 (63.62)
Former	114,596 (4.28)	19,708 (4.80)	10,187 (5.19)	965 (5.33)
Unknown	607,720 (22.69)	77,943 (18.97)	35,715 (18.21)	3,287 (18.15)
Townsend deprivation index, n (%)				
1: Lowest	677,724 (26.39)	102,924 (26.20)	46,708 (24.99)	4,685 (27.26)
2: Low	564,890 (22.00)	84,924 (21.61)	40,579 (21.71)	3,821 (22.23)
3: Moderate	534,554 (20.82)	81,331 (20.70)	39,255 (21.00)	3,566 (20.75)
4: High	468,773 (18.25)	73,004 (18.58)	35,452 (18.97)	3,038 (17.67)
5: Highest	322,027 (12.54)	50,711 (12.91)	24,936 (13.34)	2,079 (12.09)
Unknown	110,920 (4.14)	17,973 (4.37)	9,171 (4.68)	926 (5.11)
Person-time (y), median (IQR)	5.0 (2.1-9.2)	4.9 (2.1-9.2)	5.2 (2.2-9.4)	5.4 (2.1-10.4)
History of asthma, n (%)	346,024 (12.92)	80,267 (19.54)	42,608 (21.73)	4,584 (25.30)
History of allergic rhinitis, n (%)	266,083 (9.93)	66,023 (16.07)	29,926 (15.26)	3,062 (16.90)

BMI, drinking, and smoking status were not examined in the pediatric cohort because of high rates of missing data.
*Patients with AD are reported within the highest severity group they belonged to during follow-up.

BMI, smoking and drinking, and socioeconomic status were similar between patients with AD and those without AD. Duration of follow-up was 5 years on average, with slightly longer follow-up among those with severe AD. The subcohort of asthmatic patients included 346,024 patients without AD (12.9% of the total non-AD adult cohort) and 127,459 patients with AD (20.4% of the total AD adult cohort). Compared with the overall cohort, the asthmatic subcohort was slightly younger (median age, 37-42 years) and had shorter follow-up time (4.4-4.9 years) (Table II).

TABLE II. Baseline characteristics of subcohort of patients with history of asthma in THIN database (1994-2015)

Characteristics	No AD	Mild AD	Moderate AD	Severe AD
Pediatric cohort	N = 169,679	N = 49,782	N = 6,094	N = 1,222
Age (y), median (IQR)	9 (5-13)	9 (5-13)	12 (8-15)	9 (6-12)
Sex, n (%)				
Female	67,278 (39.65)	21,507 (43.20)	2,786 (45.72)	509 (41.65)
Male	102,401 (60.35)	28,275 (56.80)	3,308 (54.28)	713 (58.35)
Townsend deprivation index, n (%)				
1: Lowest	36,036 (22.25)	10,768 (22.75)	1,250 (21.54)	264 (22.78)
2: Low	31,356 (19.36)	9,158 (19.35)	1,161 (20.01)	246 (21.23)
3: Moderate	33,461 (20.66)	9,764 (20.63)	1,229 (21.18)	233 (20.10)
4: High	33,852 (20.90)	10,029 (21.19)	1,215 (20.94)	215 (18.55)
5: Highest	27,248 (16.82)	7,613 (16.08)	948 (16.34)	201 (17.34)
Unknown	7,726 (4.55)	2,450 (4.92)	291 (4.78)	63 (5.16)
Person-time (y), median (IQR)	6.8 (3.1-11.5)	7.2 (3.2-11.8)	6.8 (3.3-11.0)	10.2 (4.3-14.2)
History of allergic rhinitis, n (%)	23,127 (13.63)	9,422 (18.93)	1,453 (23.84)	292 (23.90)
History of asthma exacerbation,* n (%)	55,354 (32.62)	17,356 (34.86)	2,463 (40.42)	596 (48.77)
Adult cohort	N = 346,024	N = 80,267	N = 42,608	N = 4,584
Age (y), median (IQR)	42 (27-63)	37 (25-56)	41 (28-60)	37 (26-57)
Sex, n (%)				
Female	188,738 (54.54)	50,416 (62.81)	24,139 (56.65)	2,669 (58.22)
Male	157,286 (45.46)	29,851 (37.19)	18,469 (43.35)	1,915 (41.78)
BMI (kg/m^2), n (%)				
Underweight (<18)	12,950 (3.74)	2,898 (3.61)	1,142 (2.68)	174 (3.80)
Normal (18.5-24.9)	113,365 (32.76)	29,515 (36.77)	14,721 (34.55)	1,809 (39.46)
Overweight (25-29.9)	90,852 (26.26)	20,280 (25.27)	11,504 (27.00)	1,150 (25.09)
Obese (30-34.9)	42,558 (12.30)	9,630 (12.00)	5,508 (12.93)	493 (10.75)
Severely obese (35-39.9)	16,771 (4.85)	3,970 (4.95)	2,120 (4.98)	198 (4.32)
Morbidly obese (>40)	9,521 (2.75)	2,378 (2.96)	1,383 (3.25)	135 (2.95)
Unknown	60,007 (17.34)	11,596 (14.45)	6,230 (14.62)	625 (13.63)
Smoking status, n (%)				
Never	161,762 (46.75)	39,282 (48.94)	19,419 (45.58)	2,278 (49.69)
Current	76,044 (21.98)	17,731 (22.09)	9,719 (22.81)	970 (21.16)
Former	84,255 (24.35)	19,035 (23.71)	11,094 (26.04)	1,070 (23.34)
Unknown	23,963 (6.93)	4,219 (5.26)	2,376 (5.58)	266 (5.80)
Drinking status, n (%)				
Never	38,259 (11.06)	9,458 (11.78)	5,037 (11.82)	561 (12.24)
Current	209,365 (60.51)	50,317 (62.69)	27,281 (64.03)	2,917 (63.63)
Former	17,548 (5.07)	4,061 (5.06)	2,245 (5.27)	233 (5.08)
Unknown	80,852 (23.37)	16,431 (20.47)	8,045 (18.88)	873 (19.04)
Townsend deprivation index, n (%)				
1: Lowest	81,095 (24.40)	18,593 (24.25)	9,543 (23.53)	1,088 (25.21)
2: Low	69,645 (20.96)	15,726 (20.51)	8,339 (20.56)	989 (22.91)
3: Moderate	70,289 (21.15)	16,112 (21.02)	8,566 (21.12)	882 (20.44)
4: High	65,474 (19.70)	15,308 (19.97)	8,224 (20.27)	808 (18.72)
5: Highest	45,843 (13.79)	10,921 (14.25)	5,891 (14.52)	549 (12.72)
Unknown	13,678 (3.95)	3,607 (4.49)	2,045 (4.80)	268 (5.85)
Person-time (y), median (IQR)	4.5 (1.9, 8.3)	4.4 (1.8, 8.6)	4.8 (2.0, 8.9)	4.9 (1.8, 9.9)
History of allergic rhinitis, n (%)	77,369 (22.36)	24,300 (30.27)	12,297 (28.86)	1,456 (31.76)
History of asthma exacerbation,* n (%)	149,342 (43.16)	34,467 (42.94)	20,404 (47.89)	2,806 (61.21)

*Defined by specific diagnosis codes for asthma exacerbation.

Incidence rates of asthma, asthma exacerbations, and asthma hospitalizations among adults were higher in the presence of AD and increased with greater AD severity (Table III). Adjusted for age, sex, socioeconomic status, BMI, smoking and alcohol status, and history of allergic rhinitis, the risk of incident asthma was 38% higher overall among patients with AD compared with those without AD (HR, 1.38; 95% CI, 1.36-1.40). When stratified by AD severity, patients with mild AD had a 27% greater risk of asthma, whereas those with moderate or severe AD had a 52% to 58% greater risk of

TABLE III. Crude incidence rates per 1000 person-years and 95% CI for new-onset asthma among patients in full cohort and for asthma exacerbation and asthma-related hospitalization events among asthmatic patients in subcohort

	Incidence rates, per 1000 person-years							
	Pediatric cohort				Adult cohort			
Outcome	No AD	Mild AD	Moderate AD	Severe AD	No AD	Mild AD	Moderate AD	Severe AD
Asthma	8.41 (8.35-8.47)	17.16 (16.97-17.36)	21.99 (21.31-22.69)	30.40 (28.79-32.10)	4.10 (4.06-4.13)	5.53 (5.42-5.64)	6.70 (6.55-6.85)	6.73 (6.30-7.18)
Asthma exacerbation*	10.09 (9.93-10.25)	16.66 (16.27-17.05)	20.22 (19.21-21.29)	26.04 (23.80-28.49)	12.80 (12.64-12.96)	15.06 (14.66-15.46)	17.05 (16.57-17.54)	17.24 (15.99-18.58)
Asthma-related hospitalization†	3.00 (2.92-3.09)	4.76 (4.57-4.96)	6.76 (6.23-7.34)	8.50 (7.37-9.80)	6.09 (5.99-6.20)	6.54 (6.30-6.79)	7.89 (7.59-8.21)	8.91 (8.09-9.81)

*Defined by specific diagnosis code for asthma exacerbation.
†Defined by hospitalization within 14 d after asthma diagnosis code.

asthma (Figure 1). Among adults with asthma, the risk of asthma exacerbation was 21% higher overall in adults with AD compared with those without AD, and more severe AD was associated with increasingly greater risk of asthma exacerbation (mild AD: HR, 1.13 [95% CI, 1.10-1.17]; moderate AD: HR, 1.30 [95% CI, 1.26-1.34]; severe AD: HR, 1.37 [95% CI, 1.27-1.48]). Similar effects were observed for asthma-related hospitalization in the asthmatic subcohort (Figure 1). Overall, 1843 excess exacerbations and 891 excess hospitalizations were attributable to AD.

Similar to the pediatric cohort, when asthma exacerbation was alternatively defined by asthma diagnosis code with a systemic corticosteroid prescription, the effects of AD and AD severity on asthma exacerbation risk remained similar. Other sensitivity analyses also led to similar findings as the primary analyses (Table IV).

DISCUSSION

In this study, we observed significantly higher risk of incident asthma, asthma exacerbations, and hospitalizations among patients with AD. AD was associated with a 96% increased risk of asthma among children and a 38% increased risk among adults. The risk of asthma exacerbation or hospitalization was 50% to 195% higher in children and 13% to 44% higher in adults with AD compared with patients with asthma but without AD. In addition, the magnitude of these risks increased in parallel with AD severity, whereby patients with moderate to severe AD had the highest risk for incident asthma and asthma exacerbation outcomes.

Our findings of increased risk of incident asthma diagnosis among children with AD align with the results of previous cohort studies including several birth cohorts.[7,10,20,33] In a meta-analysis of 13 prospective cohort studies, the prevalence of asthma at age 6 years was 30% to 36% among children with AD, and the pooled odds ratio for asthma after AD onset was 2.14 (95% CI, 1.67-2.75) among the birth cohort studies.[7] However, this systematic review focused primarily on cohort studies of young children who developed AD before age 4 years. We also observed an increasing risk of incident asthma with AD severity, similar to previous studies. However, previous studies that examined AD severity were primarily cohort studies that collected data via parent-reported symptoms, unlike our study that more objectively defined severity on the basis of treatments and referrals.[13,34,35]

Unlike most previous cohort studies focused on pediatric populations, we also evaluated asthma risk among adults. Although incident asthma risk remained significantly elevated among adults with AD compared with adults without AD, the magnitude of risk was lower than that in children, suggesting that the atopic march may occur less commonly among older patients with AD and also aligning with previous research showing lower risk of asthma among individuals with later-onset AD.[36,37] It has been postulated that adult AD and pediatric AD are distinct endotypes,[38] and underlying molecular differences in cytokine activation and epidermal barrier changes could account for the variation in asthma risk between children and adults. It is also possible that asthma endotypes arising in adulthood are more heterogeneous, with only certain asthma subtypes being more associated with AD in adults.[39] In one of the few cohort studies investigating the atopic march in adulthood, childhood-onset AD was associated with new-onset "atopic" asthma—defined

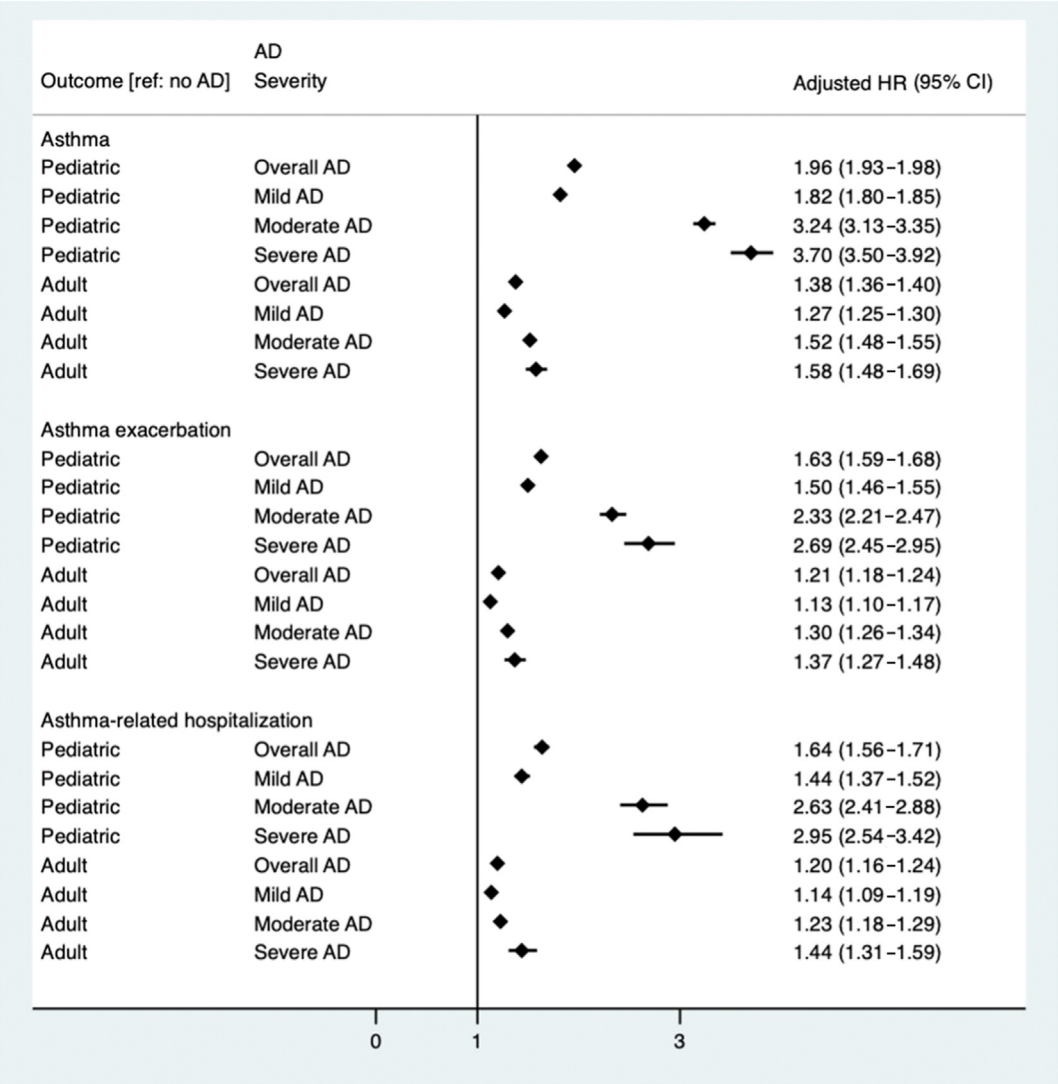

FIGURE 1. Adjustedrisk of asthma, asthma exacerbations, and asthma-related hospitalizations in the pediatric and adult cohorts in THIN database (1994-2015). Pediatric models were adjusted for age, sex, allergic rhinitis, and Townsend index. Adult models were adjusted for age, sex, allergic rhinitis, Townsend index, BMI, smoking, and alcohol status.

by positive skin prick test result to aeroallergen(s)—by middle age but not with "nonatopic" asthma.[19] Finally, there may be overlap or misclassification between asthma and chronic obstructive pulmonary disease among adults that could have contributed to our findings.

Our findings suggest that the presence of AD, especially when more severe, increases not only the risk of developing asthma but also the severity of the asthma. Few previous studies have measured the risk of asthma exacerbation or hospitalization relative to AD and AD severity. One South Korean population-based cohort study using claims data showed that AD was associated with more frequent asthma exacerbations among adults with mild or moderate asthma, although results in the severe asthma group were not statistically significant because of small sample size (n = 233); however, this study did not examine the impact of AD severity on pediatric patients.[40] Previous cross-sectional studies have similarly found increased use of oral corticosteroids, increased emergency visits for asthma, and inadequate asthma control among children with AD.[41] Moreover, null mutations in the filaggrin gene (*FLG*), which are highly associated with AD and with more severe or persistent AD, appear to be associated with worse asthma severity.[42]

Asthma development is more common among patients with early-onset and persistent AD, null mutations in *FLG*, and allergic polysensitization, all of which likely contribute to the clinical severity of AD and progression through the atopic march.[9,11,12,34,35,43,44] Although the exact mechanisms underlying the atopic march require further characterization, shared pathophysiological links between asthma and AD likely contribute.[45] Thymic stromal lymphopoietin, a T_H2 cytokine expressed by keratinocytes and systemic biomarker of skin barrier defects, has been shown to trigger bronchial hyperresponsiveness, whereas its deletion prevents the atopic march from occurring.[45] Meanwhile, superantigen enterotoxin B, produced by *Staphylococcus aureus*,

TABLE IV. Sensitivity analyses for new-onset asthma among patients in full cohort and for asthma exacerbation events among asthmatic patients in subcohort

	Adjusted HR* (95% CI) (reference: no AD)									
	Pediatric cohort					Adult cohort				
Outcome	N	Overall AD	Mild AD	Moderate AD	Severe AD	N	Overall AD	Mild AD	Moderate AD	Severe AD
New-onset asthma in full cohort										
Primary analysis	1,888,247	1.96 (1.93-1.98)	1.82 (1.80-1.85)	3.24 (3.13-3.35)	3.70 (3.50-3.92)	2,711,096	1.38 (1.36-1.40)	1.27 (1.25-1.30)	1.52 (1.48-1.55)	1.58 (1.48-1.69)
Restricted to patients seen at least yearly during follow-up	1,639,134	1.85 (1.82-1.87)	1.72 (1.70-1.75)	2.97 (2.88-3.07)	3.43 (3.24-3.63)	2,493,235	1.35 (1.33-1.37)	1.25 (1.22-1.27)	1.48 (1.45-1.52)	1.54 (1.44-1.64)
Restricted to patients with ≥5 y of follow-up	941,729	1.97 (1.94-2.00)	1.82 (1.80-1.85)	3.26 (3.14-3.38)	3.72 (3.50-3.96)	1,384,225	1.36 (1.34-1.39)	1.26 (1.23-1.29)	1.49 (1.46-1.54)	1.57 (1.46-1.69)
Restricted to patients followed for ≥1 y before cohort entry	1,130,282	1.68 (1.65-1.72)	1.60 (1.56-1.63)	2.46 (2.34-2.60)	3.03 (2.73-3.36)	2,350,999	1.35 (1.33-1.38)	1.26 (1.23-1.29)	1.47 (1.43-1.51)	1.55 (1.44-1.67)
Asthma exacerbation† in asthmatic subcohort										
Primary analysis	298,880	1.63 (1.59-1.68)	1.50 (1.46-1.55)	2.33 (2.21-2.47)	2.69 (2.45-2.95)	473,806	1.21 (1.18-1.24)	1.13 (1.10-1.17)	1.30 (1.26-1.34)	1.37 (1.27-1.48)
Outcome defined by systemic corticosteroid prescription within 3 d of asthma code	288,505	1.62 (1.58-1.67)	1.49 (1.44-1.53)	2.37 (2.24-2.50)	2.68 (2.44-2.94)	438,072	1.24 (1.22-1.27)	1.13 (1.10-1.16)	1.34 (1.30-1.38)	1.67 (1.56-1.78)
Restricted to patients seen at least yearly during follow-up	281,964	1.60 (1.55-1.64)	1.47 (1.43-1.51)	2.25 (2.12-2.38)	2.62 (2.38-2.87)	451,273	1.20 (1.17-1.23)	1.12 (1.09-1.15)	1.28 (1.24-1.32)	1.35 (1.25-1.45)
Restricted to patients with ≥5 y of follow-up	205,776	1.64 (1.59-1.69)	1.50 (1.45-1.55)	2.34 (2.20-2.48)	2.71 (2.46-2.99)	249,231	1.20 (1.17-1.23)	1.11 (1.08-1.15)	1.29 (1.24-1.33)	1.38 (1.27-1.50)
Restricted to patients followed for ≥1 y before cohort entry	221,082	1.46 (1.41-1.51)	1.32 (1.27-1.37)	2.19 (2.04-2.35)	2.43 (2.13-2.77)	403,848	1.19 (1.16-1.22)	1.12 (1.09-1.16)	1.27 (1.23-1.31)	1.31 (1.20-1.44)
Asthma-related hospitalization‡ in asthmatic subcohort										
Primary analysis	315,040	1.64 (1.56-1.71)	1.44 (1.37-1.52)	2.63 (2.41-2.88)	2.95 (2.54-3.42)	511,650	1.20 (1.16-1.24)	1.14 (1.09-1.19)	1.23 (1.18-1.29)	1.44 (1.31-1.59)
Restricted to patients seen at least yearly during follow-up	297,183	1.60 (1.53-1.68)	1.41 (1.34-1.49)	2.54 (2.33-2.78)	2.88 (2.49-3.34)	487,747	1.19 (1.15-1.23)	1.13 (1.08-1.18)	1.22 (1.17-1.27)	1.43 (1.29-1.57)
Restricted to patients with ≥5 y of follow-up	215,580	1.69 (1.60-1.77)	1.47 (1.39-1.56)	2.71 (2.46-2.98)	3.10 (2.66-3.63)	266,405	1.19 (1.15-1.23)	1.13 (1.07-1.18)	1.21 (1.16-1.27)	1.44 (1.30-1.61)
Restricted to patients followed for ≥1 y before cohort entry	235,002	1.42 (1.33-1.51)	1.24 (1.16-1.33)	2.21 (1.96-2.49)	2.69 (2.19-3.30)	436,086	1.15 (1.11-1.19)	1.10 (1.05-1.15)	1.18 (1.13-1.24)	1.36 (1.21-1.52)

*Adjusted for age, sex, Townsend score, and history of allergic rhinitis in both pediatric and adult cohorts and additionally adjusted for BMI, smoking, and alcohol status in adult cohort.
†Defined by specific diagnosis code for asthma exacerbation.
‡Defined by hospitalization within 14 d after asthma diagnosis code.

which often colonizes the skin of patients with AD, synergistically drives eczematous skin changes and promotes airway hyperreactivity and lung inflammation on allergen exposure.[45]

Although AD is traditionally considered an atopic disease akin to asthma, it has also been linked to many other nonatopic comorbidities. In other studies using the same or similar cohorts as in our present study, AD has been associated with an 18% to 52% increased risk of infectious outcomes such as herpes simplex virus or varicella zoster virus infection and serious infections[46]; 19% to 27% increased risk of dementia[47]; 14% to 48% increased risk of depression, anxiety, and obsessive compulsive disorder[48,49]; 19% to 48% increased risk of lymphoma[50]; and 21% to 27% increased risk of myocardial infarction or stroke,[51,52] and there is a 62% increased risk of mortality[53] in adults with severe AD. Notably, the 38% to 96% increased risk of asthma observed in our cohort of patients with AD is not exceedingly different than that of some of these nonatopic comorbidities. More research on the association of AD with nonatopic disorders, including nonatopic forms of asthma, may help clarify the degrees to which AD is a risk factor for both recognized atopic and less recognized nonatopic comorbidities.

Strengths of our study include its large sample size, longitudinal nature, examination of asthma risk by AD severity, and inclusion of both adults and children. Unlike previous cohort studies that focus on early-childhood-onset AD in children, our study analyzes risk in the later childhood years and how AD severity defined by treatment (rather than patient-reported symptoms) contributes to this risk. We additionally analyze asthma risk among adults, enabling direct comparisons of effect size between pediatric and adult populations. Finally, our study is one of the few cohort studies to measure risk of asthma exacerbations or hospitalizations in patients with AD.

However, several potential limitations are noted. First, misclassification of AD severity is possible; however, using treatment as a proxy measure is a common approach because direct severity measures are unavailable in routinely collected electronic health data.[26,50] The time-updated definitions for AD severity in this study may also result in misclassification for a waxing and waning disease such as AD; some patients who are defined as having moderate or severe AD may experience subsequent improvement. Such misclassification would be expected to bias HRs toward the null and may have an impact on our findings, particularly for children who may experience improvement in AD symptoms over time. Ascertainment bias is another potential concern because patients with AD may have more frequent medical visits or tests, which could lead to earlier diagnosis of asthma and related symptoms. However, sensitivity analyses limited to patients with annual GP visits led to similar findings. Finally, the duration of study follow-up was short, but sensitivity analyses restricted to patients with at least 5 years of follow-up demonstrated similar results.

AD is associated with higher incident risk of asthma, consistent with the model of the atopic march, and both the presence and severity of AD increase risk for asthma-related exacerbation and hospitalization. However, these associations are much more pronounced in children than in adults. Further work is thus needed to understand the relationships between various endotypes of AD and asthma and how they may differ by age. As novel immunomodulatory medications for AD continue to emerge, their effects on asthma development and severity will be of great interest, with the hope that future therapies may curtail progression along the atopic march.

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TABLE E1. Pediatric cohort sensitivity analyses restricted to only pediatric-onset outcomes (occurring at age <18 y)

Pediatric outcomes	Overall AD	Mild AD	Moderate AD	Severe AD
New-onset asthma in full cohort				
Primary analysis	1.96 (1.93-1.98)	1.82 (1.80-1.85)	3.24 (3.13-3.35)	3.70 (3.50-3.92)
Restricted to pediatric-onset asthma outcome	1.98 (1.95-2.00)	1.84 (1.82-1.87)	3.33 (3.21-3.44)	3.75 (3.54-3.97)
Asthma exacerbation in asthmatic subcohort				
Primary analysis	1.63 (1.59-1.68)	1.50 (1.46-1.55)	2.33 (2.21-2.47)	2.69 (2.45-2.95)
Restricted to pediatric-onset asthma	1.62 (1.58-1.67)	1.51 (1.47-1.56)	2.28 (2.14-2.42)	2.60 (2.34-2.88)
Asthma-related hospitalization in asthmatic subcohort				
Primary analysis	1.64 (1.56-1.71)	1.44 (1.37-1.52)	2.63 (2.41-2.88)	2.95 (2.54-3.42)
Restricted to pediatric-onset asthma	1.63 (1.55-1.72)	1.46 (1.38-1.54)	2.80 (2.53-3.09)	2.67 (2.24-3.17)

Values represent adjusted HR (95% CI).

TABLE E2. Pediatric cohort sensitivity analyses stratified by age <4 y and ≥4 y

Pediatric outcomes	Overall AD	Mild AD	Moderate AD	Severe AD
New-onset asthma in full cohort				
Primary analysis	1.96 (1.93-1.98)	1.82 (1.80-1.85)	3.24 (3.13-3.35)	3.70 (3.50-3.92)
Restricted to patients aged <4 y	2.15 (2.11-2.19)	2.01 (1.98-2.05)	4.03 (3.84-4.23)	4.03 (3.74-4.33)
Restricted to patients aged ≥4 y	1.73 (1.70-1.77)	1.60 (1.56-1.63)	2.66 (2.54-2.78)	3.29 (3.01-3.59)
Asthma exacerbation in asthmatic subcohort				
Primary analysis	1.63 (1.59-1.68)	1.50 (1.46-1.55)	2.33 (2.21-2.47)	2.69 (2.45-2.95)
Restricted to patients aged <4 y	1.69 (1.60-1.79)	1.61 (1.52-1.70)	2.28 (1.99-2.60)	2.77 (2.30-3.34)
Restricted to patients aged ≥4 y	1.57 (1.52-1.62)	1.43 (1.38-1.48)	2.25 (2.12-2.39)	2.59 (2.32-2.88)
Asthma-related hospitalization in asthmatic subcohort				
Primary analysis	1.64 (1.56-1.71)	1.44 (1.37-1.52)	2.63 (2.41-2.88)	2.95 (2.54-3.42)
Restricted to patients aged <4 y	1.63 (1.50-1.79)	1.51 (1.38-1.66)	2.82 (2.32-3.43)	2.50 (1.84-3.41)
Restricted to patients aged ≥4 y	1.57 (1.49-1.66)	1.37 (1.29-1.45)	2.43 (2.20-2.68)	2.96 (2.50-3.51)

Values represent adjusted HR (95% CI).