Original Article

Incidence of Cardiovascular Disease and Venous Thromboembolism in Patients With Atopic Dermatitis

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What is already known about this topic? Atopic dermatitis (AD) may increase risk for atherothrombotic and cardiovascular (CV) disease via systemic inflammation, lifestyle factors, or treatments, but prior studies of CV outcomes have been inconsistent and studies on thromboembolic outcomes are sparse.

What does this article add to our knowledge? Atopic dermatitis was associated with higher risk of venous thromboembolism. Severe AD was associated with higher risk for stroke and diabetes in both children and adults and also myocardial infarction and dyslipidemia in adults.

How does this study impact current management guidelines? Atopic dermatitis, particularly when severe, is associated with increased risks of venous thromboembolism and CV disease, which may influence the monitoring of patients and selection of treatments for AD.

BACKGROUND: Atopic dermatitis (AD) may increase risk for atherothrombotic and cardiovascular (CV) disease.
OBJECTIVE: Determine CV disease and venous thromboembolism risk among patients with AD.
METHODS: Cohort study using electronic health data from U.K. general practices in 1994 to 2015. Children (<18 y) and adults (≥18 y) with AD were matched to patients without AD on age, same practice, and encounter date. Treatments and specialist referrals served as proxies of AD severity. Outcomes were incident myocardial infarction, cerebrovascular accident (CVA), diabetes, hypertension, dyslipidemia, deep vein thrombosis (DVT), and pulmonary embolism. Cox regression analysis was used to compare outcomes in AD versus non-AD patients.
RESULTS: Comparing 409,341 children with AD (93.2% mild, 5.5% moderate, and 1.3% severe) to 1,809,029 unaffected children, AD was associated with higher risk of DVT (hazard ratio [HR] 1.23; 95% confidence interval [95% CI] 1.02−1.48) and severe AD was associated with higher risk of CVA (HR 2.43;

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Abbreviations used
AD- Atopic dermatitis
BMI- Body mass index
CV- Cardiovascular
CVA- Cerebrovascular accident
DVT- Deep vein thrombosis
EHR- Electronic health record
GP- General practitioner
HR- Hazard ratio
IQR- Interquartile range
MI- Myocardial infarction
PE- Pulmonary embolism
PY- person-years
STROBE- STrengthening the Reporting of OBservational studies in Epidemiology
THIN- The Health Improvement Network
VTE- Venous thromboembolism

95% CI 1.13−5.22) and diabetes (HR 1.46; 95% CI 1.06−2.01). Comparing 625,083 adults with AD (65.7% mild, 31.4% moderate, and 2.9% severe) to 2,678,888 unaffected adults, AD, especially when severe, was associated with higher risk of DVT (HR 1.14; 95% CI 1.11−1.18; and HR 1.64; 95% CI 1.49−1.82, respectively) and small but increased risks of CVA, diabetes, and dyslipidemia. Adults with severe AD had higher risk of myocardial infarction (HR 1.27; 95% CI 1.15−1.39), CVA (HR 1.21; 95% CI 1.13−1.30), diabetes (HR 1.15; 95% CI 1.09−1.22), dyslipidemia (HR 1.11; 95% CI 1.06−1.17), and pulmonary embolism (HR 1.39; 95% CI 1.21−1.60) compared with adults without AD.

CONCLUSIONS: Atopic dermatitis, particularly when severe, is associated with small but increased risks of CV risk factors and events and significantly increased risk of venous thromboembolism.

Key words: *Atopic dermatitis; Cardiovascular; Diabetes; Hypertension; Dyslipidemia; Deep vein thrombosis; Pulmonary embolism; Cerebrovascular accident; Stroke; Myocardial infarction*

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin condition with a lifetime prevalence of up to 20%.[1] It has been posited that the systemic inflammatory component of AD may increase risk for atherothrombotic events and cardiovascular (CV) disease.[2-5] Lifestyle factors and treatments for AD may also contribute.[6,7] Prior studies suggest that low physical activity, poor sleep, and active smoking, which may mediate or modify CV risk, are more common in patients with AD.[8] Treatments for AD such as cyclosporine and corticosteroids are associated with hypertension,[7] although 1 meta-analysis showed that using any systemic treatments (biologics, methotrexate, retinoids, or oral agents) was associated with decreased risk of CV events in patients with AD.[6]

To date, the relationship between AD and CV events (eg, myocardial infarction [MI] and stroke) and risk factors (eg, diabetes and hypertension) in adults remains unclear because previous findings are inconsistent,[7,9-13] with 1 meta-analysis finding no association between AD and diabetes, hypertension, MI, or stroke.[11] Cohort studies have also reported conflicting results on thromboembolic disease risk in adults with AD.[14-16] In addition, studies on CV risk factors have been primarily cross-sectional, and few cohort studies have evaluated dyslipidemia risk with AD. The American Academy of Dermatology's guidelines indicate only moderate certainty that AD in adults is probably associated with hypertension, dyslipidemia, coronary artery disease, and thromboembolic diseases, whereas the connection with MI and stroke is uncertain but may follow a severity gradient.[17] Meanwhile, pediatric studies of any CV outcomes and risk factors in AD are lacking.

Thus, we conducted a population-based cohort study to examine the incidence of CV risk factors (diabetes, hypertension, and dyslipidemia), as well as CV events (MI, cerebrovascular accident [CVA]) and venous thromboembolism (VTE) among children and adults with AD, hypothesizing that such outcomes increase with greater AD severity.

METHODS

We conducted a cohort study using The Health Improvement Network (THIN), an electronic health record (EHR) database of general practices in the United Kingdom that is broadly representative of the general U.K. population. The general practitioner (GP) is the primary contact for medical care in the United Kingdom, and THIN has been used extensively to study conditions including AD, CV outcomes, and thromboembolic events, among others.[18-21] Data were collected between 1994 and 2015, with the aim to analyze background risk of CV disease in patients with AD in the absence of biologic and other targeted immunomodulatory therapies that may separately modify the effect of AD on CV disease.

All patients in THIN with a diagnosis of AD were included. Atopic dermatitis was defined by the presence of 1 or more of 5 diagnostic codes for AD and 2 or more AD-related treatment codes, a validated algorithm with 86% positive predictive value for physician-confirmed AD diagnosis.[18] Each AD patient was matched to up to 5 non-AD patients based on age (±3 y), same practice, any EHR encounter within ± 6 months of the index date for the AD patient (defined as the latter of practice registration date and diagnosis date). All ages were included, with analyses stratified into pediatric (<18 y at baseline) and adult (≥18 y) cohorts. Each non-AD patient was assigned a diagnosis date within ± 6 months of the index date of the exposed patient, to ensure that AD and non-AD patients were followed by similar providers during similar time periods. Follow-up time for patients with AD began at the latest of first AD diagnosis, practice registration date, or Vision date (ie, when Vision software was implemented for data transfer to THIN, thereby ensuring good data quality). For non-AD individuals, follow-up time began at the latest of diagnosis date, practice registration date, or Vision date. Follow-up time ended at the earliest of outcome, transfer out of the practice, death, or end of study. Patients with a history of the outcome of interest at time of cohort entry were excluded from corresponding analyses.

Although not directly recorded in THIN, AD severity was estimated using treatments and referrals as proxies and defined in a time-updated manner. All patients with AD were considered to have mild disease by default. They were classified as having moderate AD at the first receipt of (1) a second potent topical corticosteroid within 1 year or (2) any topical calcineurin inhibitors, which are reserved for

moderate disease in the United Kingdom.[22] 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).[23] 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 follow-up. Although not directly validated, this approach to defining AD severity has been used in previous research and leads to estimates consistent with the literature.[9]

The primary outcomes of interest were MI, CVA, diabetes (both types 1 and 2), hypertension, dyslipidemia, deep vein thrombosis (DVT), and pulmonary embolism (PE). Outcomes were identified using Read codes, which record diagnoses, symptoms, and tests.[24] We also collected data on age, sex, socioeconomic status (ie, Townsend index, a measure of material deprivation, with higher index indicating greater deprivation), and comorbid illnesses. Body mass index (BMI), smoking, and alcohol data were available for the adult cohort.

Covariates were defined at cohort entry and AD severity and age were time-updated. Cox regression models were used to compare outcomes between patients with AD and those without, adjusted for potential confounders determined *a priori* based on biological plausibility including age, sex, socioeconomic status, BMI, smoking and drinking status, and relevant comorbidities (detailed in Figure 1). *P* values were not included to compare baseline characteristics between study groups because small absolute differences may be considered statistically significant in the context of our large sample size and do not necessarily equate clinical significance. Sensitivity analyses were conducted to address potential biases introduced by atopic comorbidities, short follow-up duration, medications, and ascertainment bias. All analysis was conducted in Stata17. The study was developed in accordance with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines, approved by the data vendor's Scientific Review Committee, and granted exemption by the University of Pennsylvania Institutional Review Board.

RESULTS

Pediatric cohort

In total, 409,431 patients with AD (93.2% mild, 5.5% moderate, and 1.3% severe) were matched to 1,809,029 patients without AD. The median age ranged from 4 to 9 years across the severity groups, and there was a slight male predominance (51%−56%) (Table 1). Socioeconomic status was generally similar across the groups. Median follow-up time was 5.0 years (interquartile range [IQR] 2.0−9.4) among non-AD patients but longer among AD patients (5.2 y [IQR 2.1−9.7], 6.0 y [IQR 2.6−10.2], and 6.9 y [IQR 2.7−12.6] for mild, moderate, and severe AD, respectively). Baseline comorbidities are shown in Table I.

Incidence of CVA, MI, DVT, and PE were extremely low (Table II). Diabetes occurred with an incidence of 0.35 in 1,000 person-years (PY) in non-AD patients, compared to 0.33, 0.36, and 0.54 per 1,000 PY in patients with mild, moderate, and severe AD, respectively. The incidence of hypertension was similar between non-AD and mild AD patients (0.17 and 0.16/1,000 PY, respectively), whereas patients with moderate and severe AD had higher rates (0.41 and 0.40/1,000 PY, respectively). Similar trends were seen for dyslipidemia, whereby moderate and severe AD groups had higher rates than the non-AD and mild AD groups (Table II).

Comparing children with AD to those without, no statistically significant association between AD and incident diabetes, hypertension, dyslipidemia, CVA, or MI was observed in adjusted models (Figure 1, *A*). However, when stratified by disease severity, severe AD was significantly associated with a 143% greater risk of CVA (hazard ratio [HR] 2.43; 95% confidence interval [95% CI] 1.13−5.22) and 46% greater risk of diabetes (HR 1.46; 95% CI 1.06−2.01) than with no AD. Whereas hypertension risk was also elevated among those with moderate AD (HR 1.23; 95% CI 1.01−1.49), a similar trend was observed among those with severe AD (HR 1.37; 95% CI 0.94−2.01). Atopic dermatitis was associated with a 23% increased risk for DVT (HR 1.23; 95% CI 1.02−1.48) but not PE (HR 0.78; 95% CI 0.58−1.05). The risk for DVT was primarily driven by the mild (HR 1.28; 95% CI 1.04−1.57) and severe (HR 2.13; 95%CI 1.17−3.87) AD groups.

Adult cohort

In total, 625,083 patients with AD (65.7% mild, 31.4% moderate, and 2.9% severe) were matched to 2,678,888 patients without AD. The median age was 47 years (IQR 32−64 y) in the non-AD group and 45 to 50 years in the AD groups (Table I). Females comprised 54% of the non-AD group and 56% to 62% of the AD groups. Body mass index, smoking and drinking status, and socioeconomic status were similar between AD and non-AD groups. Study follow-up was approximately 5 years on average, with slightly longer follow-up among those with moderate or severe AD. Prevalence of medical comorbidities is shown in Table I.

Among the outcomes, hypertension occurred most commonly, with a rate of 17.6/1,000 PY in the non-AD group compared with 20.1 and 19.3/1,000 PY in the moderate and severe AD groups, respectively. The incidence of diabetes was 5.8/1,000 PY in the non-AD group, in contrast to 7.4 and 6.8/1,000 PY in the moderate and severe AD groups, respectively. Dyslipidemia, MI, CVA, DVT, and PE also developed at higher rates in the moderate and severe AD groups than in the mild or non-AD groups (Table II).

In multivariable models, AD was associated with a small but increased risk of CVA overall (HR 1.04; 95% CI 1.02−1.06), with the severe AD group having a 21% increased risk compared with the non-AD group (HR 1.21;95% CI 1.13−1.30) (Figure 1, *B*). Similarly, AD was associated with a small increased risk of diabetes and dyslipidemia (HR 1.05; 95% CI 1.03−1.06 and HR 1.03; 95% CI 1.02−1.04, respectively), particularly among patients with severe AD (HR 1.15; 95% CI 1.09−1.22 and HR 1.11;95% CI 1.06−1.17, respectively). Whereas no difference was detected for mild or moderate AD, severe AD was also associated with a 27% increased risk of MI (HR 1.27; 95% CI 1.15−1.39). Mild AD was associated with slightly lower risk of hypertension (HR 0.97; 95% CI 0.96−0.98) and severe AD was associated with slightly higher risk of hypertension (HR 1.05; 95% CI 1.01−1.10). Atopic dermatitis was associated with an overall 14% higher risk of DVT (HR 1.1; 95% CI 1.11−1.18), with the risk being 64% higher in the severe AD group (HR 1.64; 95% CI 1.49−1.82). Similarly, PE risk was 39% greater among patients with severe AD (HR 1.39; 95% CI 1.21−1.60); however, no significant differences were detected for moderate AD, whereas mild AD was conversely associated

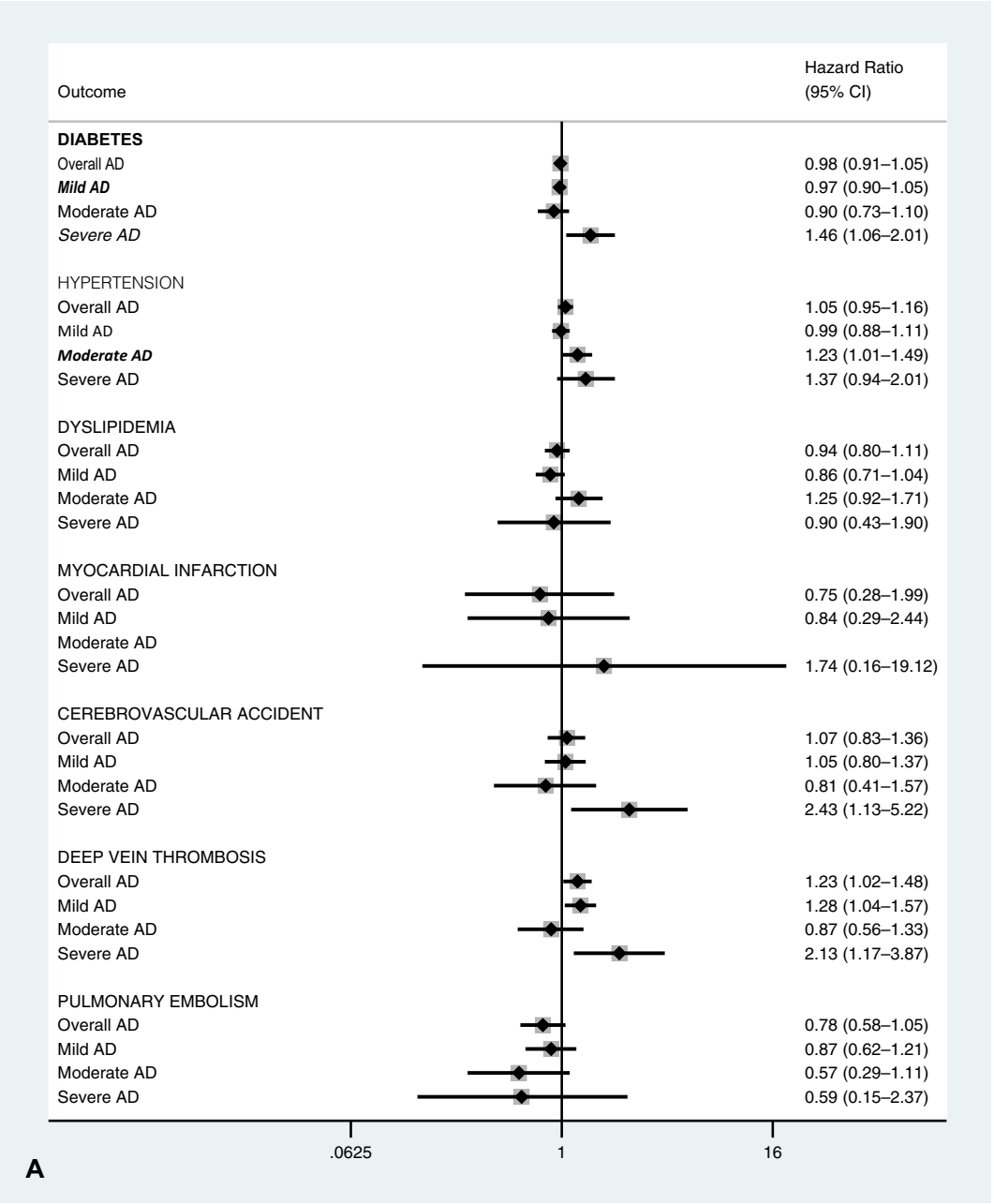

FIGURE 1. (**A**) Adjusted rate of CV risk factors and events and VTE outcomes in pediatric cohorts with vs without AD in THIN databases, 1994−2015. All models were adjusted for age, sex and Townsend score. Models for individual outcomes were additionally adjusted for covariates as: Diabetes—history of dyslipidemia and/or hypertension. Hypertension—history of diabetes, dyslipidemia, chronic kidney disease, depression, and/or anxiety. Dyslipidemia—history of diabetes, peripheral vascular disease, MI, CVA, and/or hypertension. Myocardial infarction—history of diabetes, hypertension, dyslipidemia, chronic kidney disease, depression, anxiety, allergic rhinitis, and/or asthma. Cerebrovascular accident—history of diabetes, hypertension, dyslipidemia, chronic kidney disease, depression, anxiety, allergic rhinitis, and/or asthma. Deep vein thrombosis and pulmonary embolism—history of malignancy, congestive heart failure, respiratory failure, chronic obstructive pulmonary disease, pregnancy, hormonal therapy, chronic kidney disease, MI, atrial fibrillation, diabetes, hypertension, and/or liver disease. (**B**) Adjusted rate of CV risk factors and events and VTE outcomes in adult cohorts with and without AD in THIN databases, 1994−2015. All models were adjusted for age, sex, Townsend score, BMI, and smoking and alcohol status. Models for individual outcomes were additionally adjusted for covariates as: Diabetes—history of dyslipidemia and/or hypertension. Hypertension—history of diabetes, dyslipidemia, chronic kidney disease, depression, and/or anxiety. Dyslipidemia—history of diabetes, peripheral vascular disease, MI, CVA, and/or hypertension. Myocardial infarction—history of diabetes, hypertension, dyslipidemia, chronic kidney disease, depression, anxiety, allergic rhinitis, and/or asthma. Cerebrovascular accident—history of diabetes, hypertension, dyslipidemia, chronic kidney disease, depression, anxiety, allergic rhinitis, and/or asthma. Deep vein thrombosis and pulmonary embolism—history of malignancy, congestive heart failure, respiratory failure, chronic obstructive pulmonary disease, pregnancy, hormonal therapy, chronic kidney disease, MI, atrial fibrillation, diabetes, hypertension, and/or liver disease.

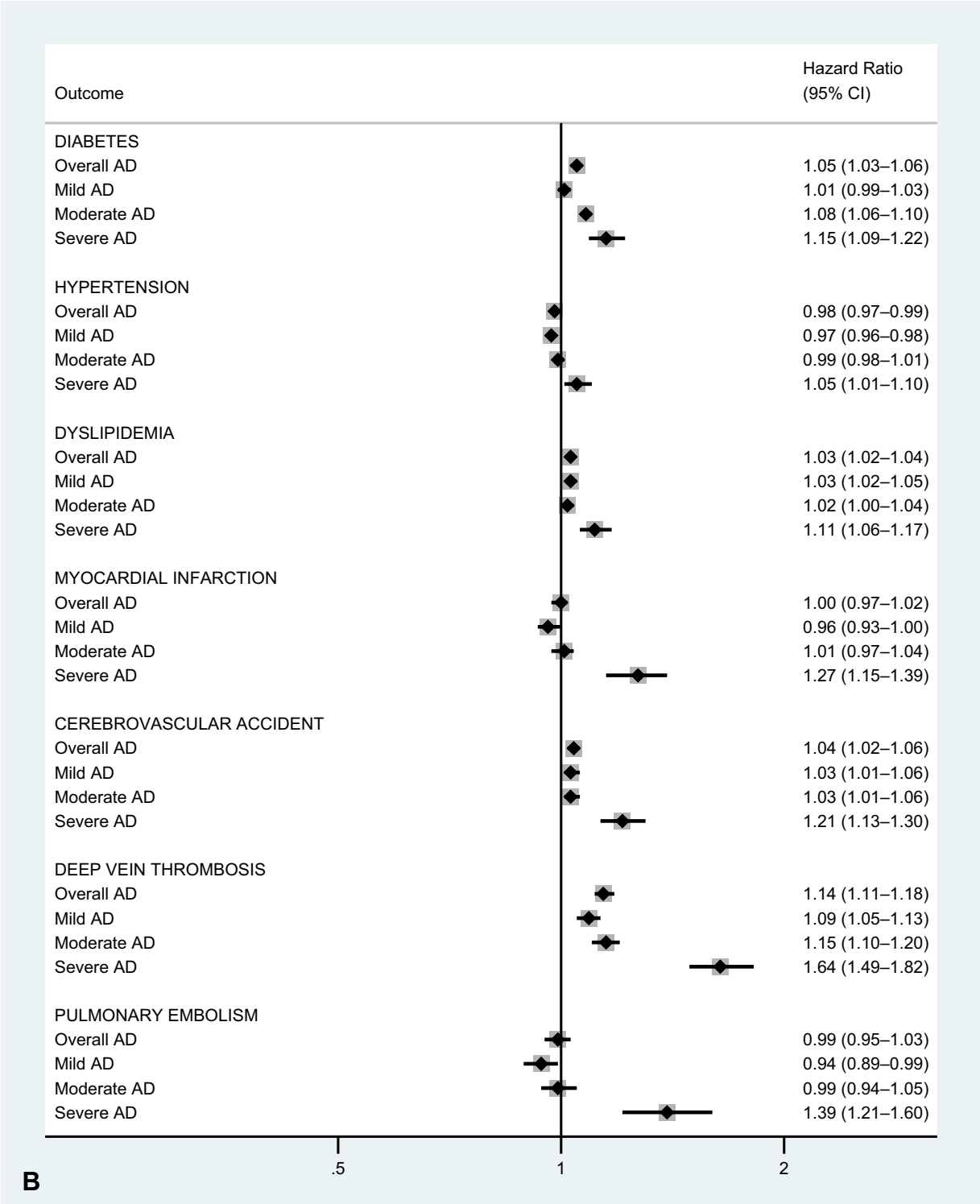

FIGURE 1. (*CONTINUED*).

with a 6% lower risk of PE compared with no AD (HR 0.94; 95% CI 0.89−0.99).

Sensitivity analyses restricting to only patients with yearly GP follow-up, at least 5 years' follow-up, or at least 1 year of observation time prior to cohort entry did not differ from the primary findings (Table E1; available in this article's Online Repository at www.jaci-inpractice.org). Analyses excluding patients with history of asthma or allergic rhinitis and patients receiving systemic immunosuppressants for AD also led to similar results.

TABLE I. Baseline characteristics of pediatric and adult cohorts in THIN database, 1994−2015

Characteristic, n (%)	Control	All AD	Mild AD	Moderate AD	Severe AD
Pediatric cohort	n = 1,809,029	n = 409,431	n = 381,678	n = 22,433	n = 5,320
Age, median (IQR), y	4 (2, 9)	4 (1, 9)	4 (1, 8)	9 (4, 14)	5 (1, 10)
Sex					
Female	872,279 (48.22)	198,071 (48.38)	184,682 (48.39)	11,054 (49.28)	2,335 (43.89)
Male	936,750 (51.78)	211,360 (51.62)	196,996 (51.61)	11,379 (50.72)	29,85 (56.11)
Townsend deprivation index					
1-Lowest	424,409 (24.71)	95,839 (24.77)	89,820 (24.89)	4,768 (22.55)	1,251 (25.00)
2-Low	340,677 (19.84)	77,154 (19.94)	71,979 (19.95)	4,106 (19.42)	1,069 (21.37)
3-Moderate	355,559 (20.70)	80,845 (20.89)	75,261 (20.86)	4,551 (21.52)	1,033 (20.65)
4-High	339,336 (19.76)	75,865 (19.60)	70,649 (19.58)	4,316 (20.41)	900 (17.99)
5-Highest	257,540 (14.99)	57,270 (14.80)	53,113 (14.72)	3,407 (16.11)	750 (14.99)
Unknown	91,508 (5.06)	22,458 (5.49)	20,856 (5.46)	1,285 (5.73)	317 (5.96)
Person-time (y), median (IQR)	4.99 (2.0−9.4)	5.29 (2.15−9.81)	5.22 (2.1−9.7)	6.02 (2.6−10.2)	6.89 (2.7−12.6)
Allergic rhinitis	75,050 (4.15)	27,326 (6.67)	23,935 (6.27)	2,870 (12.79)	521 (9.79)
Asthma	169,679 (9.38)	57,098 (13.95)	49,782 (13.04)	6,094 (27.17)	1,222 (22.97)
Anxiety	8,752 (0.48)	2,146 (0.52)	1,886 (0.49)	226 (1.01)	34 (0.64)
Depression	4,318 (0.24)	970 (0.24)	797 (0.21)	158 (0.70)	15 (0.28)
Atrial fibrillation	59 (0.00)	5 (0.00)	4 (0.00)	1 (0.00)	0 (0.00)
Congestive heart failure	768 (0.04)	141 (0.03)	134 (0.04)	2 (0.01)	5 (0.09)
Diabetes	2,708 (0.15)	434 (0.11)	395 (0.10)	31 (0.14)	8 (0.15)
Dyslipidemia	211 (0.01)	32 (0.01)	22 (0.01)	5 (0.02)	5 (0.09)
Hypertension	523 (0.03)	118 (0.03)	95 (0.02)	10 (0.04)	13 (0.24)
Peripheral vascular disease	206 (0.01)	44 (0.01)	39 (0.01)	5 (0.02)	0 (0.00)
History of CVA	633 (0.03)	141 (0.03)	126 (0.03)	12 (0.05)	3 (0.06)
History of MI	7 (0.00)	2 (0.00)	2 (0.00)	0 (0.00)	0 (0.00)
History of DVT	138 (0.01)	30 (0.01)	24 (0.01)	5 (0.02)	1 (0.02)
History of pulmonary embolism	25 (0.00)	3 (0.00)	3 (0.00)	0 (0.00)	0 (0.00)
Chronic kidney disease	825 (0.05)	167 (0.04)	140 (0.04)	8 (0.04)	19 (0.36)
Chronic obstructive pulmonary disease	188 (0.01)	53 (0.01)	47 (0.01)	3 (0.01)	3 (0.06)
Respiratory failure	6,860 (0.38)	1,355 (0.33)	1,272 (0.33)	56 (0.25)	27 (0.51)
History of malignancy	1,736 (0.10)	342 (0.08)	307 (0.08)	24 (0.11)	11 (0.21)
OCP or hormonal therapy use	24647 (1.36)	6468 (1.58)	5353 (1.40)	1034 (4.61)	81 (1.52)
Adult cohort	n = 2,678,888	n = 625,083	n = 410,867	n = 196,101	n = 18,115
Age, median (IQR), y	47 (32, 64)	47 (31, 65)	45 (30, 63)	50 (34, 68)	47 (32, 63)
Sex					
Female	1,445,589 (53.96)	1,821,800 (55.14)	256,071 (62.32)	109,404 (55.79)	10,736 (59.27)
Male	1,233,299 (46.04)	1,482,171 (44.86)	154,796 (37.68)	86,697 (44.21)	7,379 (40.73)
BMI, kg/m^2					
Underweight (<18)	72,655 (2.71)	88,834 (2.69)	11,504 (2.80)	4,150 (2.12)	525 (2.90)
Normal (18.5−24.9)	911,449 (34.02)	1,136,916 (34.41)	152,480 (37.11)	66,015 (33.66)	6,972 (38.49)
Overweight (25−29.9)	707,292 (26.40)	877,805 (26.57)	109,693 (26.70)	56,021 (28.57)	4,799 (26.49)
Obese (30−34.9)	285,567 (10.66)	356,553 (10.79)	44,998 (10.95)	24,088 (12.28)	1,900 (10.49)
Severely obese (35−39.9)	94,373 (3.52)	119,232 (3.61)	15,720 (3.83)	8,486 (4.33)	653 (3.60)
Morbidly obese (>40)	44,721 (1.67)	57,930 (1.75)	8,341 (2.03)	4,525 (2.31)	343 (1.89)
Unknown	562,831 (21.01)	666,701 (20.18)	68,131 (16.58)	32,816 (16.73)	2,923 (16.14)
Smoking status					
Never	1,293,811 (48.30)	1,598,629 (48.39)	206,577 (50.28)	89,588 (45.68)	8,653 (47.77)
Current	576,463 (21.52)	709,427 (21.47)	84,855 (20.65)	44,195 (22.54)	3,914 (21.61)
Former	548,828 (20.49)	693,936 (21.00)	92,290 (22.46)	48,636 (24.80)	4,182 (23.09)
Unknown	259,786 (9.70)	301,979 (9.14)	27,145 (6.61)	13,682 (6.98)	1,366 (7.54)

(continued)

TABLE I. *(Continued)*

Characteristic, n (%)	Control	All AD	Mild AD	Moderate AD	Severe AD
Drinking status					
Never	300,614 (11.22)	77,824 (12.45)	51,208 (12.46)	24,278 (12.38)	2,338 (12.91)
Current	1,655,958 (61.82)	399,454 (63.90)	262,008 (63.77)	125,921 (64.21)	11,525 (63.62)
Former	114,596 (4.28)	30,860 (4.94)	19,708 (4.80)	10,187 (5.19)	965 (5.33)
Unknown	607,720 (22.69)	116,945 (18.71)	77,943 (18.97)	35,715 (18.21)	3,287 (18.15)
Townsend deprivation index					
1-Lowest	677,724 (26.39)	154,317 (25.85)	102,924 (26.20)	46,708 (24.99)	4,685 (27.26)
2-Low	564,890 (22.00)	129,324 (21.66)	84,924 (21.61)	40,579 (21.71)	3,821 (22.23)
3-Moderate	534,554 (20.82)	124,152 (20.80)	81,331 (20.70)	39,255 (21.00)	3,566 (20.75)
4-High	468,773 (18.25)	111,494 (18.68)	73,004 (18.58)	35,452 (18.97)	3,038 (17.67)
5-Highest	322,027 (12.54)	77,726 (13.02)	50,711 (12.91)	24,936 (13.34)	2,079 (12.09)
Unknown	110,920 (4.14)	28,070 (4.49)	17,973 (4.37)	9,171 (4.68)	926 (5.11)
Person-time (y) median (IQR)	4.96 (2.09−9.18)	5.02 (2.09−9.36)	4.94 (2.05−9.24)	5.20 (2.204−9.44)	5.41 (2.14−10.44)
Allergic rhinitis	266,083 (9.93)	99,011 (15.84)	66,023 (16.07)	29,926 (15.26)	3,062 (16.90)
Asthma	346,024 (12.92)	127,459 (20.39)	80,267 (19.54)	42,608 (21.73)	4,584 (25.30)
Anxiety	379,810 (14.18)	486,729 (14.73)	71,528 (17.41)	32,646 (16.65)	2,745 (15.15)
Depression	526,849 (19.67)	148,075 (23.69)	97,510 (23.73)	46,401 (23.66)	4,164 (22.99)
Atrial fibrillation	59,294 (2.21)	15,395 (2.46)	9,231 (2.25)	5,764 (2.94)	400 (2.21)
Congestive heart failure	45,960 (1.72)	12,772 (2.04)	7,529 (1.83)	4,874 (2.49)	369 (2.04)
Diabetes	139,798 (5.22)	34,221 (5.47)	21,014 (5.11)	12,276 (6.26)	931 (5.14)
Dyslipidemia	200,780 (7.49)	49,073 (7.85)	30,490 (7.42)	17,209 (8.78)	1,374 (7.58)
Hypertension	519,270 (19.38)	125,521 (20.08)	76,728 (18.67)	45,089 (22.99)	3,704 (20.45)
Peripheral vascular disease	37,866 (1.41)	10,693 (1.71)	6,262 (1.52)	4,134 (2.11)	297 (1.64)
History of CVA	78,044 (2.91)	20,291 (3.25)	12,266 (2.99)	7,495 (3.82)	530 (2.93)
History of MI	62,446 (2.33)	15,716 (2.51)	9,230 (2.25)	6,048 (3.08)	438 (2.42)
History of DVT	33,201 (1.24)	10,164 (1.63)	6,180 (1.50)	3,549 (1.81)	435 (2.40)
History of PE	16,507 (0.62)	4,520 (0.72)	2,752 (0.67)	1,556 (0.79)	212 (1.17)
Chronic kidney disease	73,550 (2.75)	18,683 (2.99)	10,835 (2.64)	6,903 (3.52)	945 (5.22)
Chronic obstructive pulmonary disease	62,537 (2.33)	17,908 (2.86)	10,253 (2.50)	7,064 (3.60)	591 (3.26)
Respiratory failure	2,462 (0.09)	696 (0.11)	448 (0.11)	223 (0.11)	25 (0.14)
History of malignancy	173,235 (6.47)	45,234 (7.24)	28,665 (6.98)	15,239 (7.77)	1,330 (7.34)
OCP or hormonal therapy use	791,294 (29.54)	225,727 (36.11)	156,082 (37.99)	63,241 (32.25)	6,404 (35.35)

OCP, Oral contraceptive.

DISCUSSION

In this study, overall AD was associated with increased risk of DVT in children and increased risk of diabetes, dyslipidemia, CVA, and DVT in adults. Specifically, moderate or severe AD was associated with increased risk of diabetes, hypertension, DVT, and CVA in both children and adults as well as dyslipidemia, MI, and PE in adults.

The relationship between AD and CV risk factors has been inconsistent in previous studies. One meta-analysis of studies conducted in adults found no association between AD and type 2 diabetes or hypertension, whereas another did identify an association between moderate-to-severe AD and hypertension.[11,25] Select cohort studies have also observed small but statistically significantly elevated risk of hypertension in patients with AD similar in magnitude to our findings.[12] A cross-sectional study evaluating CV risk among Canadian adults with AD found inverse associations between AD and hypertension and type 2 diabetes,[26] whereas U.S. studies have found 30%−40% greater odds of hypertension, diabetes, and dyslipidemia in adults with AD and higher blood pressure in children with AD compared with individuals without AD.[7,27] In our current study, we observed a marginally increased risk of diabetes, hypertension, and dyslipidemia in adults with moderate or severe AD but no statistically significant associations in adults with mild AD or among most children with AD. Studies examining the association between AD and major adverse CV events, including MI and stroke, have also demonstrated mixed findings. Although some cross-sectional studies of U.S. adults have found higher odds of MI, stroke, coronary artery disease, and peripheral vascular disease in individuals with AD compared with no AD,[28] 1 cross-sectional analysis of U.S. female nurses found no association between AD and nonfatal MI or stroke after adjustment for CV risk factors and atopic comorbidities, and 1 Canadian study found a lower odds of MI and stroke in patients with AD.[26,29]

TABLE II. Incidence rates and 95% CIs of CV risk factors and events and VTE outcomes in adult and pediatric cohorts in THIN database, 1994–2015

CV risk factor	Incidence rate (95% CI), per 1,000 PY			
	Pediatric cohort			
Outcome	No AD	Mild AD	Moderate AD	Severe AD
Diabetes	0.35 (0.34–0.36)	0.33 (0.31–0.36)	0.36 (0.30–0.44)	0.54 (0.40–0.74)
Hypertension	0.17 (0.17–0.18)	0.16 (0.14–0.17)	0.41 (0.34–0.49)	0.40 (0.28–0.58)
Dyslipidemia	0.07 (0.07–0.08)	0.06 (0.05–0.07)	0.16 (0.12–0.22)	0.10 (0.05–0.21)
MI	0.00 (0.00–0.00)	0.00 (0.00–0.00)	*	0.01 (0.00–0.10)
CVA	0.03 (0.03–0.03)	0.03 (0.02–0.04)	0.03 (0.02–0.06)	0.10 (0.05–0.21)
DVT	0.05 (0.04–0.05)	0.05 (0.04–0.06)	0.08 (0.05–0.12)	0.16 (0.09–0.28)
PE	0.02 (0.02–0.03)	0.02 (0.01–0.02)	0.03 (0.02–0.06)	0.03 (0.01–0.11)
	Adult cohort			
Outcome	No AD	Mild AD	Moderate AD	Severe AD
Diabetes	5.84 (5.80–5.88)	5.46 (5.36–5.56)	7.35 (7.21–7.50)	6.79 (6.41–7.19)
Hypertension	17.60 (17.52–17.67)	16.17 (15.98–16.36)	20.10 (19.83–20.38)	19.30 (18.57–20.05)
Dyslipidemia	9.52 (9.47–9.57)	9.39 (9.25–9.53)	10.86 (10.68–11.04)	10.66 (10.17–11.17)
MI	2.02 (2.00–2.05)	1.78 (1.72–1.83)	2.47 (2.39–2.55)	2.50 (2.28–2.75)
CVA	3.83 (3.79–3.86)	3.71 (3.62–3.79)	4.83 (4.72–4.94)	4.48 (4.18–4.80)
DVT	1.32 (1.31–1.34)	1.39 (1.34–1.44)	1.76 (1.69–1.83)	2.19 (1.99–2.42)
PE	0.79 (0.78–0.81)	0.72 (0.69–0.76)	0.93 (0.88–0.98)	1.13 (0.99–1.30)

*No events.

Cohort studies have shown similarly inconsistent findings but have more commonly found associations between AD and CV outcomes, particularly with increasing AD severity.[30] Cohort studies in Taiwan[31] and Sweden[32] have found greater risk of MI and ischemic stroke in adults with moderate-to-severe AD. In contrast, German[12] and Danish[10] cohort studies have found no significant associations between AD and MI or stroke after adjustment for lifestyle factors. In a more recent population-based study of U.K. adults, severe and active AD was associated with a 20% increased risk of stroke and a 30% to 40% increased risk of MI that persisted after adjustment for BMI, smoking, alcohol use, and other comorbidities.[9] Our study similarly found a 21% increased risk of stroke and a 27% increased risk of MI in adults with severe AD. Unlike previous studies, however, our study also included a pediatric cohort, finding a very rare incidence of MI and stroke in children but a notable 2.4-fold increased risk of stroke among children with severe AD compared with no AD.

Fewer studies have examined VTE risk in AD.[15,16,33] One cross-sectional study using U.S. inpatient data found a 28% greater odds of DVT and an 8% greater odds of PE in hospitalized adults with AD than in adults without AD.[33] However, hospitalized individuals are likely at greater risk for VTE, thereby limiting the generalizability of those estimates to the larger AD population. A recent cohort study using U.S. administrative claims data found a 24% greater risk of VTE in adults with moderate-to-severe AD than with no AD, but the association no longer remained after adjusting for health care utilization, medications, and other comorbidities.[16] In contrast, another study of adults with AD in a commercially insured claims database showed no increased risk for VTE (HR 1.19; 95% CI 0.95–1.48).[15] In our study population, we observed a 9% to 64% increased risk of DVT in adults with AD, with greatest risk among those with severe AD, and a 39% higher risk of PE in adults with severe AD. Among the pediatric cohort, children with mild AD demonstrated a 28% higher risk of DVT and those with severe AD had a 2-fold increased risk of DVT but no increased risk for PE. These findings call for further investigation of potential links between AD and VTE and their underlying mechanisms, particularly because newer medications for AD, such as Janus kinase inhibitors, have been associated with increased reports of thromboembolic events.[34]

Taking our results together with the literature, the current study supports an association between AD and a variety of CV outcomes in both children and adults, particularly when AD is severe. However, further research is needed to understand the pathophysiological mechanisms driving these associations. One possibility is that lifestyle factors, such as sleep or smoking, may mediate or moderate the development of CV disease.[7] Although we adjusted for potential confounders including BMI, smoking, and alcohol use, it is possible that residual confounding remains. Medications for AD, such as cyclosporine, systemic corticosteroids, or chronic use of topical corticosteroids, could also contribute to conditions such as diabetes and hypertension.[35-37] Another possibility is that chronic systemic inflammation in AD drives atherothrombotic and other CV outcomes via inflammatory changes in vascular walls and oxidative stress, as supported by studies associating CV disease with other inflammatory conditions such as psoriasis and rheumatoid arthritis.[38-41] Increased platelet activation and altered plasma fibrin clot properties have been observed in patients with AD, which may lead to decreased fibrinolysis and increased risk of thrombosis.[3,40]

Our study's strengths include its large sample size, longitudinal nature, examination of effects by AD severity, and adjustment for potential confounders, which has not been routinely done in in prior studies. However, there are potential limitations to note. Because treatments were used as proxies for AD severity, we cannot separate severity effects from treatment effects. Misclassification of AD severity is also possible using this method; however, this approach is commonly taken in

epidemiological investigations of AD because direct severity measures are not routinely captured in EHR data.[9,42] Although AD severity was treated as a time-updated variable to allow for escalation over time, we recognize that severity may also de-escalate with time given AD's waxing-and-waning nature. Nevertheless, we chose this methodology because it is more conservative and we would expect any such misclassification to bias our results toward the null. The latter may have indeed contributed to the weak or absent dose-response relationships we observed between the mild and the moderate AD groups for many outcomes. Outcome misclassification is also possible, but we would expect it to be nondifferential with respect to the exposure because GPs were unaware of our study hypothesis. Ascertainment bias is another potential limitation if patients with AD were more likely to see their GPs; however, our sensitivity analyses restricted to only patients seen at least annually yielded similar results. Finally, our study had relatively short follow-up duration, which may preclude the capture of CV outcomes that tend to arise in older age, especially in the pediatric cohort. Nevertheless, sensitivity analyses restricted to patients with at least 5 years of follow-up showed similar findings to the primary analyses.

In conclusion, moderate-to-severe AD appears to be associated with a small but increased risk of several CV risk factors and events and a significantly elevated risk of VTE. Research is needed to further dissect the mechanisms driving these associations and confirm our observations of elevated DVT risk in both children and adults with AD. Our findings also suggest a greater risk of diabetes, hypertension, and stroke among children with moderate-to-severe AD; thus, continued investigations of CV risk in pediatric populations are needed to help inform monitoring and counseling of young patients with AD. As a whole, AD is underrecognized as a possible contributor to CV risk in existing guidelines and literature in both children and adults.[43-45] With novel immunomodulatory treatments for AD continuing to emerge, an understanding of background CV and thromboembolic risk in patients with AD will be critical for informing treatment selection for patients and evaluating the impact of novel treatments on these outcomes.

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TABLE E1. Sensitivity analyses restricted to cohorts without atopic comorbidities or immunosuppressive therapies and cohorts meeting additional follow-up criteria*

	Adjusted HR (95% CI) [reference: no AD]							
	Pediatric cohort				Adult cohort			
Outcome†	Overall AD	Mild AD	Moderate AD	Severe AD	Overall AD	Mild AD	Moderate AD	Severe AD
Diabetes								
Primary analysis	0.98 (0.91−1.05)	0.97 (0.90−1.05)	0.90 (0.73−1.10)	1.46 (1.06−2.01)	1.05 (1.03−1.06)	1.01 (0.10−1.03)	1.08 (1.06−1.10)	1.15 (1.09−1.22)
Excluding patients with asthma or allergic rhinitis	0.97 (0.89−1.05)	0.96 (0.88−1.05)	0.87 (0.67−1.12)	1.45 (0.98−2.15)	1.03 (1.01−1.05)	0.99 (0.97−1.02)	1.07 (1.04−1.09)	1.14 (1.06−1.22)
Restricted to patients seen at least yearly during follow-up	0.91 (0.85−0.98)	0.91 (0.84−0.99)	0.82 (0.67−1.01)	1.34 (0.98−1.85)	1.03 (1.02−1.05)	1.00 (0.98−1.02)	1.06 (1.04−1.09)	1.13 (1.07−1.20)
Restricted to patients with at least 5 y of follow-up	0.97 (0.89−1.05)	0.97 (0.89−1.06)	0.86 (0.69−1.07)	1.24 (0.87−1.78)	1.04 (1.03−1.06)	1.00 (0.98−1.03)	1.08 (1.05−1.10)	1.13 (1.06−1.21)
Restricted to patients followed for ≥ 1 y prior to cohort entry	0.98 (0.91−1.05)	0.97 (0.90−1.05)	0.90 (0.73−1.10)	1.46 (1.06−2.01)	1.05 (1.03−1.06)	1.01 (0.99−1.03)	1.08 (1.06−1.10)	1.15 (1.09−1.22)
Excluding patients with immunosuppressive therapies‡	0.98 (0.90−1.05)	0.98 (0.90−1.06)	0.89 (0.73−1.10)	1.30 (0.91−1.84)	1.05 (1.04−1.07)	1.02 (0.98−1.04)	1.09 (1.06−1.11)	1.13 (1.05−1.21)
Hypertension								
Primary analysis	1.05 (0.95−1.16)	0.99 (0.88−1.11)	1.23 (1.01−1.49)	1.37 (0.94−2.01)	0.98 (0.97−0.99)	0.97 (0.96−0.98)	0.99 (0.98−1.01)	1.05 (1.01−1.10)
Exclusion of pregnancy-related hypertension	1.02 (0.92−1.13)	0.98 (0.87−1.11)	1.10 (0.90−1.35)	1.34 (0.91−1.97)	0.97 (0.96−0.98)	0.95 (0.94−0.97)	0.97 (0.96−0.99)	1.03 (0.99−1.07)
Excluding patients with asthma or allergic rhinitis	1.03 (0.91−1.17)	0.97 (0.84−1.12)	1.24 (0.96−1.60)	1.40 (0.84−2.32)	0.99 (0.97−1.00)	0.98 (0.96−0.99)	0.99 (0.97−1.01)	1.06 (1.01−1.11)
Restricted to patients seen at least yearly during follow-up	1.01 (0.91−1.12)	0.95 (0.84−1.07)	1.17 (0.96−1.42)	1.30 (0.89−1.91)	0.97 (0.96−0.97)	0.95 (0.94−0.97)	0.97 (0.96−0.99)	1.03 (0.99−1.07)
Restricted to patients with at least 5 y of follow-up	1.06 (0.95−1.17)	1.00 (0.88−1.13)	1.22 (1.003−1.49)	1.32 (0.89−1.96)	0.98 (0.97−0.99)	0.97 (0.96−0.99)	0.99 (0.97−1.002)	1.04 (0.997−1.08)
Restricted to patients followed for ≥ 1 y prior to cohort entry	1.05 (0.95−1.16)	0.99 (0.88−1.11)	1.23 (1.01−1.49)	1.37 (0.94−2.01)	0.98 (0.97−0.99)	0.97 (0.96−0.98)	0.99 (0.98−1.01)	1.05 (1.01−1.10)
Excluding patients with immunosuppressive therapies‡	1.07 (0.97−1.19)	1.02 (0.91−1.14)	1.23 (1.01−1.49)	1.30 (0.86−1.97)	0.98 (0.97−0.99)	0.97 (0.96−0.99)	1.00 (0.98−1.01)	1.00 (0.95−1.04)
Dyslipidemia								
Primary analysis	0.94 (0.80−1.11)	0.86 (0.71−1.04)	1.25 (0.92−1.71)	0.90 (0.43−1.90)	1.03 (1.02−1.04)	1.03 (1.02−1.05)	1.02 (1.00−1.04)	1.11 (1.06−1.17)
Excluding patients with asthma or allergic rhinitis	0.97 (0.79−1.19)	0.92 (0.73−1.16)	1.16 (0.75−1.80)	1.27 (0.52−3.05)	1.04 (1.02−1.05)	1.03 (1.01−1.05)	1.03 (1.01−1.05)	1.12 (1.05−1.18)

(continued)

TABLE E1. *(Continued)*

	Adjusted HR (95% CI) [reference: no AD]							
	Pediatric cohort				Adult cohort			
Outcome[†]	Overall AD	Mild AD	Moderate AD	Severe AD	Overall AD	Mild AD	Moderate AD	Severe AD
Restricted to patients seen at least yearly during follow-up	0.90 (0.76−1.06)	0.83 (0.69−1.01)	1.20 (0.88−1.63)	0.86 (0.41−1.81)	1.02 (1.002−1.027)	1.018 (1.00−1.03)	1.00 (0.99−1.02)	1.09 (1.04−1.14)
Restricted to patients with at least 5 y of follow-up	0.91 (0.76−1.08)	0.81 (0.66−0.99)	1.31 (0.96−1.79)	0.93 (0.44−1.96)	1.02 (1.01−1.03)	1.02 (1.004−1.04)	1.01 (0.99−1.03)	1.11 (1.05−1.16)
Restricted to patients followed for $\geq$ 1 y prior to cohort entry	0.94 (0.80−1.11)	0.86 (0.71−1.04)	1.25 (0.92−1.71)	0.90 (0.43−1.90)	1.03 (1.02−1.04)	1.03 (1.02−1.05)	1.02 (1.00−1.04)	1.11 (1.06−1.17)
Excluding patients with immunosuppressive therapies[‡]	0.94 (0.79−1.11)	0.88 (0.73−1.07)	1.25 (0.92−1.70)	0.56 (0.21−1.50)	1.03 (1.02−1.05)	1.04 (1.02−1.05)	1.02 (1.00−1.04)	1.12 (1.05−1.18)
Myocardial infarction								
Primary analysis	0.75 (0.28−1.99)	0.84 (0.29−2.44)	NA	1.74 (0.16−19.12)	1.00 (0.97−1.02)	0.96 (0.93−0.997)	1.01 (0.97−1.04)	1.27 (1.15−1.39)
Excluding patients with asthma or allergic rhinitis	NA	NA	NA	NA	1.00 (0.97−1.03)	0.96 (0.93−1.00)	1.02 (0.98−1.06)	1.21 (1.08−1.35)
Restricted to patients seen at least yearly during follow-up	0.72 (0.27−1.91)	0.81 (0.28−2.35)	NA	1.69 (0.16−17.96)	0.99 (0.96−1.01)	0.96 (0.92−0.99)	1.00 (0.96−1.03)	1.25 (1.14−1.37)
Restricted to patients with at least 5 y of follow-up	0.89 (0.34−2.38)	0.98 (0.33−2.87)	NA	3.26 (0.43−24.58)	1.00 (0.97−1.03)	0.97 (0.93−1.01)	1.01 (0.97−1.05)	1.25 (1.13−1.39)
Restricted to patients followed for $\geq$ 1 y prior to cohort entry	0.75 (0.28−1.99)	0.84 (0.29−2.44)	NA	1.74 (0.15−19.12)	1.00 (0.97−1.02)	0.96 (0.93−0.997)	1.01 (0.97−1.04)	1.27 (1.15−1.39)
Excluding patients with immunosuppressive therapies[‡]	0.65 (0.23−1.89)	0.89 (0.31−2.56)	NA	NA	1.00 (0.98−1.03)	0.98 (0.94−1.01)	1.02 (0.99−1.06)	1.15 (1.02−1.29)
Cerebrovascular accident								
Primary analysis	1.07 (0.83−1.36)	1.05 (0.80−1.37)	0.81 (0.41−1.57)	2.43 (1.13−5.22)	1.04 (1.02−1.06)	1.03 (1.01−1.06)	1.03 (1.01−1.06)	1.21 (1.13−1.30)
Excluding patients with asthma or allergic rhinitis	1.23 (0.92−1.63)	1.18 (0.86−1.61)	1.05 (0.47−2.36)	3.07 (1.21−7.74)	1.04 (1.02−1.07)	1.03 (1.01−1.06)	1.03 (1.01−1.06)	1.26 (1.16−1.36)
Restricted to patients seen at least yearly during follow-up	1.01 (0.77−1.29)	0.99 (0.76−1.30)	0.76 (0.39−1.48)	2.31 (1.07−4.96)	1.03 (1.01−1.05)	1.02 (1.00−1.05)	1.02 (1.00−1.05)	1.20 (1.12−1.29)
Restricted to patients with at least 5 y of follow-up	1.05 (0.80−1.37)	1.05 (0.78−1.40)	0.75 (0.37−1.52)	2.26 (0.998−5.10)	1.05 (1.03−1.08)	1.05 (1.02−1.08)	1.05 (1.02−1.08)	1.20 (1.11−1.30)
Restricted to patients followed for $\geq$ 1 y prior to cohort entry	1.07 (0.83−1.36)	1.05 (0.80−1.37)	0.81 (0.41−1.57)	2.43 (1.13−5.22)	1.04 (1.02−1.06)	1.03 (1.01−1.06)	1.03 (1.01−1.06)	1.21 (1.13−1.30)

Excluding patients with immunosuppressive therapies‡	1.06 (0.83−1.36)	1.06 (0.81−1.39)	0.77 (0.40−1.50)	2.50 (1.11−5.63)	1.04 (1.02−1.06)	1.04 (1.01−1.06)	1.04 (1.01−1.06)	1.16 (1.07−1.27)
Deep vein thrombosis								
Primary analysis	1.23 (1.02−1.48)	1.28 (1.04−1.57)	0.87 (0.56−1.33)	2.13 (1.17−3.87)	1.14 (1.11−1.18)	1.09 (1.05−1.13)	1.15 (1.10−1.20)	1.64 (1.49−1.82)
Excluding patients with asthma or allergic rhinitis	1.20 (0.95−1.51)	1.26 (0.98−1.62)	0.91 (0.52−1.58)	1.43 (0.53−3.85)	1.14 (1.10−1.18)	1.09 (1.04−1.14)	1.15 (1.10−1.21)	1.65 (1.46−1.86)
Restricted to patients seen at least yearly during follow-up	1.18 (0.98−1.42)	1.23 (1.00−1.51)	0.83 (0.54−1.27)	2.02 (1.11−3.68)	1.13 (1.10−1.16)	1.08 (1.04−1.12)	1.14 (1.09−1.18)	1.61 (1.46−1.79)
Restricted to patients with at least 5 years of follow-up	1.16 (0.96−1.41)	1.23 (0.99−1.52)	0.73 (0.46−1.17)	2.15 (1.18−3.91)	1.14 (1.10−1.18)	1.07 (1.02−1.12)	1.17 (1.12−1.23)	1.60 (1.44−1.79)
Restricted to patients followed for $\geq$ 1 y prior to cohort entry	1.23 (1.02−1.48)	1.28 (1.04−1.57)	0.87 (0.56−1.33)	2.13 (1.17−3.87)	1.14 (1.11−1.18)	1.09 (1.05−1.13)	1.15 (1.10−1.20)	1.64 (1.49−1.82)
Excluding patients with immunosuppressive therapies‡	1.26 (1.05−1.51)	1.32 (1.07−1.62)	0.86 (0.56−1.33)	2.31 (1.27−4.20)	1.14 (1.11−1.17)	1.11 (1.06−1.15)	1.17 (1.12−1.22)	1.33 (1.17−1.52)
Pulmonary embolism								
Primary analysis	0.78 (0.58−1.05)	0.87 (0.62−1.21)	0.57 (0.29−1.11)	0.59 (0.15−2.37)	0.99 (0.95−1.03)	0.94 (0.89−0.99)	0.99 (0.94−1.05)	1.39 (1.21−1.60)
Excluding patients with asthma or allergic rhinitis	1.04 (0.72−1.50)	1.16 (0.78−1.73)	0.71 (0.29−1.73)	0.60 (0.08−4.31)	0.97 (0.93−1.02)	0.91 (0.86−0.97)	0.99 (0.93−1.06)	1.39 (1.18−1.64)
Restricted to patients seen at least yearly during follow-up	0.76 (0.56−1.02)	0.84 (0.60−1.17)	0.55 (0.28−1.07)	0.57 (0.14−2.28)	0.98 (0.94−1.02)	0.93 (0.88−0.98)	0.98 (0.93−1.04)	1.37 (1.20−1.58)
Restricted to patients with at least 5 y of follow-up	0.78 (0.57−1.05)	0.86 (0.61−1.21)	0.58 (0.30−1.12)	0.59 (0.15−2.38)	0.98 (0.93−1.02)	0.94 (0.88−0.996)	0.98 (0.92−1.05)	1.31 (1.12−1.54)
Restricted to patients followed for $\geq$ 1 y prior to cohort entry	0.78 (0.58−1.05)	0.87 (0.62−1.21)	0.57 (0.29−1.11)	0.59 (0.15−2.37)	0.99 (0.95−1.03)	0.94 (0.89−0.99)	0.99 (0.94−1.05)	1.39 (1.21−1.60)
Excluding patients with immunosuppressive therapies‡	0.81 (0.60−1.10)	0.91 (0.65−1.27)	0.58 (0.30−1.12)	0.70 (0.17−2.81)	0.99 (0.95−1.03)	0.96 (0.91−1.01)	1.01 (0.95−1.07)	1.20 (1.00−1.42)

AD, atopic dermatitis; *COPD,* chronic obstructive pulmonary disease; *HR,* hazard ratio; *NA,* not available..

Diabetes: history of dyslipidemia and/or hypertension.

Hypertension: history of diabetes, dyslipidemia, chronic kidney disease, depression, and/or anxiety.

Dyslipidemia: history of diabetes, peripheral vascular disease, myocardial infarction, cerebrovascular accident, and/or hypertension.

Myocardial infarction: history of diabetes, hypertension, dyslipidemia, chronic kidney disease, depression, anxiety, allergic rhinitis, and/or asthma.

Cerebrovascular accident: history of diabetes, hypertension, dyslipidemia, chronic kidney disease, depression, anxiety, allergic rhinitis, and/or asthma.

Deep vein thrombosis and pulmonary embolism: history of malignancy, congestive heart failure, respiratory failure, COPD, pregnancy, hormonal therapy, chronic kidney disease, myocardial infarction, atrial fibrillation, diabetes, hypertension, and/or liver disease.

*Models in the pediatric cohort were adjusted for age, sex, and Townsend score. Models in the adult cohort were adjusted for age, sex, Townsend score, body mass index, smoking, and alcohol status. Models for individual outcomes were additionally adjusted for covariates indicated in footnote †.

†Additional covariates by individual outcomes:

‡Immunosuppressive therapies excluded were azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil.