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ORIGINAL RESEARCH

The Association Between Atopic Dermatitis and Select Disease Events in Adults in the United States: A Retrospective Cohort Study in the Optum Electronic Health Records Database

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ABSTRACT

Introduction: Previous studies have reported positive associations between atopic dermatitis (AD) and select disease events; however, definitive conclusions are lacking. The aim of this study was to characterize demographic and clinical characteristics of patients with and without AD and estimate crude incidence rates (IRs) and adjusted hazard rate ratios (HRRs) of select disease events in these cohorts.

Methods: This retrospective observational analysis used Optum® Market Clarity Electronic Health Records, a US administrative healthcare database. Adults with and without AD between 2016 and 2021 with ≥ 12 months of database activity prior to index date (based on diagnosis or first treatment) were included. Each patient with AD was matched on age and index date with five patients without AD.

The AD cohort was stratified by treatment prescribed within 30 days of AD diagnosis: no AD treatment; topical corticosteroids (TCS)/topical calcineurin inhibitors (TCI) only ("TCS/TCI only"); phototherapy with/without TCS/TCI ("phototherapy"); and systemic therapy, including oral corticosteroids with/without phototherapy and with/without TCS/TCI ("systemics"). Crude IRs and adjusted HRRs of infections, malignancies, cardiovascular events,

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mental health outcomes, asthma, fracture, and death across patient subgroups were estimated.

***Results*:** The total cohort comprised 161,646 adults. Among the 25,915 patients with AD, 8384 (32.35%), 13,459 (51.94%), 366 (1.41%), and 3706 (14.30%) were included in the "no AD treatment," "TCS/TCI only," "phototherapy," and "systemics" subgroups, respectively. Crude IRs/1000 patient-years were higher among patients with AD versus those without AD for serious infections (38.35 vs. 19.21), major adverse cardiovascular events (16.51 vs. 11.82), venous thromboembolism (11.12 vs. 6.89), malignancies (excluding nonmelanoma skin cancer; 17.51 vs. 15.25), and depression (63.50 vs. 44.18); similar trends were observed after controlling for potential confounding variables. When stratified by treatment, IRs and HRRs of these events were generally higher in patients in the "systemics" subgroup versus other treatment subgroups.

***Conclusions*:** Overall, certain disease event rates were higher in the population with AD versus the population without AD, with a trend towards higher rates among patients prescribed systemic therapies compared with those prescribed TCS/TCI only. This study further informs the relationship between AD and the risk of select disease events.

Keywords: Atopic dermatitis; Electronic health records database; Disease events; Incidence rates; Hazard rate ratios; Treatment subgroups

Key Summary Points

Why carry out the study?
Atopic dermatitis (AD) is a common chronic skin disorder associated with systemic inflammation.
This retrospective US-based observational analysis of electronic health records data aimed to investigate whether AD was associated with select disease events.
What was learned from the study?
Rates of select disease events, such as infections, malignancies, cardiovascular events, mental health outcomes, asthma, fracture, and death, were higher in patients with AD versus those without AD.
Rates of these disease events were generally higher in patients receiving systemic therapies than in those using only topical corticosteroids/calcineurin inhibitors.
These results further inform clinicians about the incidence of select disease events in patients with versus without AD and may help contextualize the safety profile of AD therapies in clinical trials.

INTRODUCTION

Atopic dermatitis (AD) is an immune-mediated inflammatory skin disorder with an estimated prevalence of 5.0–10.0% among adults in the US [1–5]. Systemic inflammation underpins AD pathophysiology and is associated with upregulation of interleukin (IL)-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin protein, and interferon-γ [6–9].

Previous studies identified positive associations between AD and other atopies, allergic and immune-mediated conditions (e.g., alopecia areata, chronic urticaria and asthma), mental health outcomes, extra-cutaneous and systemic infections, cardiovascular disease, and malignancies [10–12]. While some studies have suggested the reasons for this increased risk may be multifactorial and likely due to medication and lifestyle (e.g., smoking), but not AD itself [13–15], others have suggested that AD is an independent risk factor, albeit with a very small absolute risk [16, 17].

Population-based cohort studies conducted in Europe, the US, UK, and Asia have identified an increased risk of infections and cardiovascular and malignancy events in patients with AD versus without AD [15, 18–25]. However, generalizability, the number of comorbidities assessed, and/or sample size were limited in some of these studies [15, 18, 22]. The objectives of this large

retrospective US-based electronic health records (EHR) database study were to estimate crude incidence rates (IRs) in patients with AD and age-matched controls without AD stratified by AD treatment, and to estimate hazard rate ratios (HRRs) of infections, malignancies, cardiovascular events, mental health outcomes, asthma, fracture, and death comparing patients with AD and stratified by AD treatment to patients without AD, controlling for potentially confounding variables.

METHODS

Study Design and Data Sources

Data from the US-based Optum® Market Clarity EHR database were included in this retrospective observational study. The Optum EHR database contains deidentified data from > 700 hospitals and > 7000 clinics treating > 116 million patients in the US [26–28]. Optum partners directly with medical groups, Integrated Delivery Networks, and hospital corporations to extract data from EHRs [26, 28]. Data are obtained from inpatient and ambulatory EHRs, among numerous other internal systems [27]. Demographics, diagnostic codes, and treatment information were obtained from patients with and without a diagnosis of AD during the study period (1 January 2016–31 December 2021).

Patients and Assessments

Adults (aged ≥ 18 years) with ≥ 1 inpatient or ≥ 2 outpatient AD diagnoses on two unique dates ≥ 30 days apart during the study period with ≥ 12 months of continuous database activity before the index date were eligible for inclusion. AD diagnosis was based on International Classification of Diseases (ICD) diagnosis codes (Fig. 1). Patients with AD (AD cohort) were matched by age (± 3 years of birthdate) and index date (year, month) with five randomly-selected individuals with no AD in the 12 months prior to the index date or during the study period (non-AD cohort).

The AD cohort was stratified according to treatment prescribed within 30 days of diagnosis (Fig. 1). Treatment subgroups were topical corticosteroids (TCS)/topical calcineurin inhibitors (TCI) only ("TCS/TCI only"), phototherapy with/without TCS/TCI without systemics ("phototherapy"), and systemic therapy with/without phototherapy, with/without TCS/TCI ("systemics"). Patients with AD who were not prescribed AD treatment within 30 days of index were included in the "no AD treatment" subgroup.

In the AD cohort and AD with no AD treatment subgroup, the index date was defined as the first date of AD diagnosis during the study period. For the AD treatment subgroups, the index date was defined as the first treatment date within the 30-day assessment period. The contribution to person-time for each treatment subgroup began on the date of AD treatment initiation. Patients who switched to or added treatment to treat more advanced disease (e.g., started with TCS/TCI and added phototherapy) stopped contributing person-time to the original subgroup and began contributing person-time to the new treatment subgroup at the time of switching/add on. Patients who switched/added a treatment to treat less advanced disease (e.g., systemics and then TCS/TCI) contributed person-time only to the original (more advanced) treatment subgroup. In the non-AD cohort, the index date was defined as a random date in the study period, and all patients were required to have a healthcare visit within 1 month of their assigned index date. The follow-up period for each cohort and treatment subgroup began at index and ended at the occurrence of the following events, whichever occurred first: end of the study period; first select disease event occurrence (for that event only); switch to a more advanced AD treatment (i.e., from TCS/TCI only, to phototherapy, to systemics); end of database activity; or death.

Select disease events included infections (serious infections, opportunistic infections, tuberculosis, herpes zoster, herpes simplex, coronavirus disease 2019 [COVID-19], conjunctivitis), malignancies (malignancy excluding nonmelanoma skin cancer [NMSC], lung cancer, breast cancer, melanoma, leukemia,

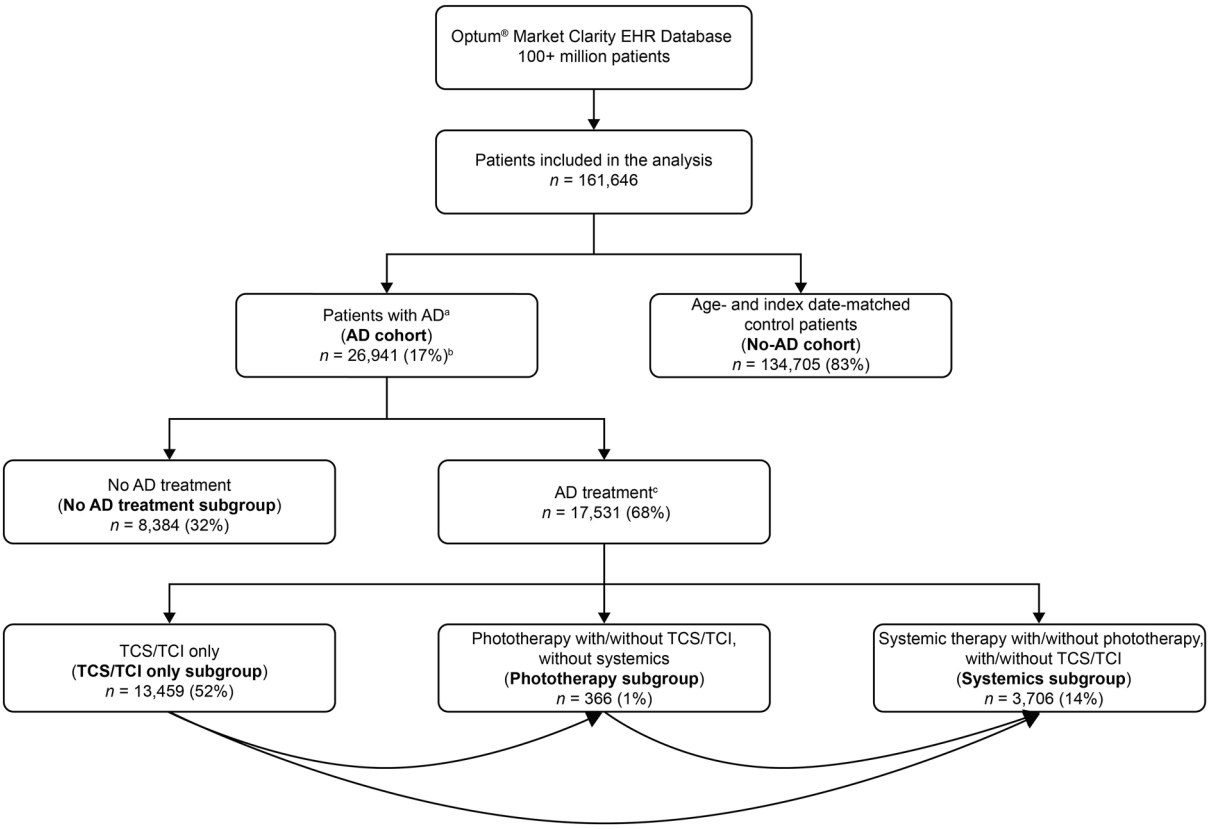


Fig. 1 Patient cohort selection schematic. [a]AD was defined according to the ICD-10 codes L20, L20.0, L20.8, L20.81, L20.82, L20.84, L20.89, and L20.9. [b]Of 26,941 patients in the AD cohort, 1026 patients were prescribed AD medication within 12 months prior to the index date but not during the 30-day follow-up period and were therefore ineligible for inclusion in any treatment subgroup. [c]Patient numbers and proportions reflect the first AD treatment group assigned within the first 30 days during the follow-up period. Systemic therapies included oral and injectable corticosteroids, immunosuppressants/immunomodulators (azathioprine, cyclosporine, interferon gamma, methotrexate, mycophenolic acid/mycophenolic mofetil), and monoclonal antibodies (dupilumab, omalizumab, rituximab). *AD* Atopic dermatitis, *EHR* electronic health records, *ICD-10* International Classification of Diseases 10th Revision, *TCS/TCI*, topical corticosteroids/topical calcineurin inhibitors

lymphoma [including cutaneous lymphoma], basal cell carcinoma [BCC], squamous cell carcinoma [SCC]), cardiovascular events (major adverse cardiovascular events [MACE]; myocardial infarction [MI], stroke, venous thromboembolism events [VTE], deep vein thrombosis [DVT], pulmonary embolism [PE], peripheral arterial disease), mental health outcomes (anxiety and depression), asthma, hospitalization due to asthma, fracture, and death.

Statistical Analysis

Descriptive statistics were calculated as means (standard deviation [SD]) and medians (range) for continuous variables and as *n* (%) for dichotomous and categorical variables. Crude IRs (95% confidence interval [CI]) per 1000 patient-years (PYs) of select disease events were estimated for the AD and non-AD cohorts based on survival analysis of time to first event. The initial occurrence of each event during the risk window was attributed to the patient to calculate IRs and HRRs; however, event-specific

follow-up ended with the initial occurrence. Patients were assessed for other events in the follow-up period, and each select disease event was assessed separately.

Multivariable Cox regression models were used to estimate HRRs (95% CI), comparing time to incident disease event between the AD and non-AD cohorts. Models were adjusted for potential confounding variables (age, sex, race, ethnicity, smoking status, body mass index [BMI], comorbid conditions, and concomitant medications) determined a priori based on previous research [21, 22, 26, 27] and assessed within the baseline period (12 months prior to index).

All analyses were performed using the Instant Health Data Analytics platform (Panalgo, Boston, USA). Imputation for missing values was not performed, and missing categorical variables were coded as "missing."

Ethical Approval

This was a retrospective database study and was not subject to ethical review.

RESULTS

Baseline Demographics

This analysis included 161,646 adults, with 26,941 (16.67%) adults in the AD cohort and 134,705 (83.33%) adults in the non-AD cohort (Table 1; Electronic Supplementary Material [ESM] Table S1). The mean (SD) patient age was 49.89 (18.53) years in the AD cohort and 49.90 (18.50) years in the non-AD cohort, and 61.67% and 60.48% of patients were female, respectively. Based on race, the AD cohort comprised 69.28% White, 17.59% Black or African American, and 4.96% Asian patients, and the non-AD cohort comprised 79.76% White, 10.22% Black or African American, and 1.88% Asian patients; 6.28% of patients in the AD cohort and 5.28% of the patients in the non-AD cohort were Hispanic. According to BMI, 33.76% and 29.78% of the AD cohort and non-AD cohort were obese (BMI ≥ 30 kg/m^2), respectively. A total of 28.69% and 25.61% of the AD cohort and non-AD cohort, respectively, were current or former smokers.

The AD cohort was further stratified according to AD treatment prescribed during the first 30 days post AD diagnosis. A total of 1026 (3.81%) patients were prescribed AD medication during the baseline period, but not during follow-up, and were therefore ineligible for inclusion in any treatment subgroup. Of the remaining 25,915 patients with AD, 8384 (32.35%), 13,459 (51.94%), 366 (1.41%), and 3706 (14.30%) were included in the "no AD treatment," "TCS/TCI only," "phototherapy," and "systemics" subgroups, respectively (Fig. 1). Allergic rhinitis and asthma were more common in the AD cohort than in the non-AD cohort (allergic rhinitis: 12.84% vs. 3.90%; asthma: 14.87% vs. 10.32%); similar patterns were observed for a variety of comorbidities and indicators of poor health (Table 1; ESM Tables S1, S2).

Crude IRs and Adjusted HRRs of Select Disease Events

Crude IRs/1000 PY for disease events within each AD treatment subgroup described below and presented in Fig. 2 focus on the AD cohort and AD treatment subgroups. The adjusted HRRs described below and presented in Table 2 compare the AD cohort and AD treatment subgroups with the non-AD cohort.

Infections

Crude IRs/1000 PY for all infections (except tuberculosis) were higher in the AD cohort versus the non-AD cohort (Fig. 2a). In the AD cohort, crude IRs/1000 PY (95% CI) ranged from 0.23 (0.15, 0.37) for tuberculosis to 38.35 (36.89, 39.87) for serious infections. IRs for serious infections were significantly higher in the systemics subgroup compared with the TCS/TCI only, phototherapy, and no AD treatment subgroups. IRs for opportunistic infections were significantly higher in the systemics subgroup compared with the TCS/TCI only and no AD

Table 1 Baseline demographics and medical history of patients with and without atopic dermatitis in the Optum® electronic health records database (2016–2021)

Baseline demographics and medical history	AD cohort (*n* = 26,941)	Non-AD cohort (*n* = 134,705)
Age at index date, years		
Mean (SD)	49.89 (18.53)	49.90 (18.50)
Median (IQR)	51.00 (34.00–64.00)	51.0 (34.00–64.00)
Sex, n (%)		
Male	10,310 (38.27)	53,136 (39.45)
Female	16,615 (61.67)	81,474 (60.48)
Race, n (%)		
White	18,664 (69.28)	107,439 (79.76)
Black or African American	4739 (17.59)	13,767 (10.22)
Asian	1337 (4.96)	2533 (1.88)
Other/unknown	2201 (8.17)	10,966 (8.14)
Ethnicity, n (%)		
Hispanic	1692 (6.28)	7109 (5.28)
Not Hispanic	22,878 (84.92)	114,322 (84.87)
Non-Hispanic White	16,591 (61.58)	96,318 (71.50)
Unknown	2371 (8.80)	13,274 (9.85)
BMI, kg/m^2, n (%)		
< 18.5	311 (1.15)	1309 (0.97)
≤ 18.5 to < 25.0	5197 (19.29)	23,978 (17.80)
≤ 25.0 to < 30.0	6222 (23.09)	28,958 (21.50)
≤ 30.0 to < 35.0	4498 (16.70)	20,385 (15.13)
≤ 35.0 to < 40.0	2400 (8.91)	10,780 (8.00)
≤ 40.0	2198 (8.16)	8954 (6.65)
Unknown	6115 (22.70)	40,341 (29.95)
BMI, kg/m^2, n (%)		
≥ 30	9096 (33.76)	40,119 (29.78)
< 30	11,730 (43.54)	54,245 (40.27)
Unknown	6115 (22.70)	40,341 (29.95)
Smoking status, n (%)		
Current	2730 (10.13)	12,807 (9.51)

Table 1 continued

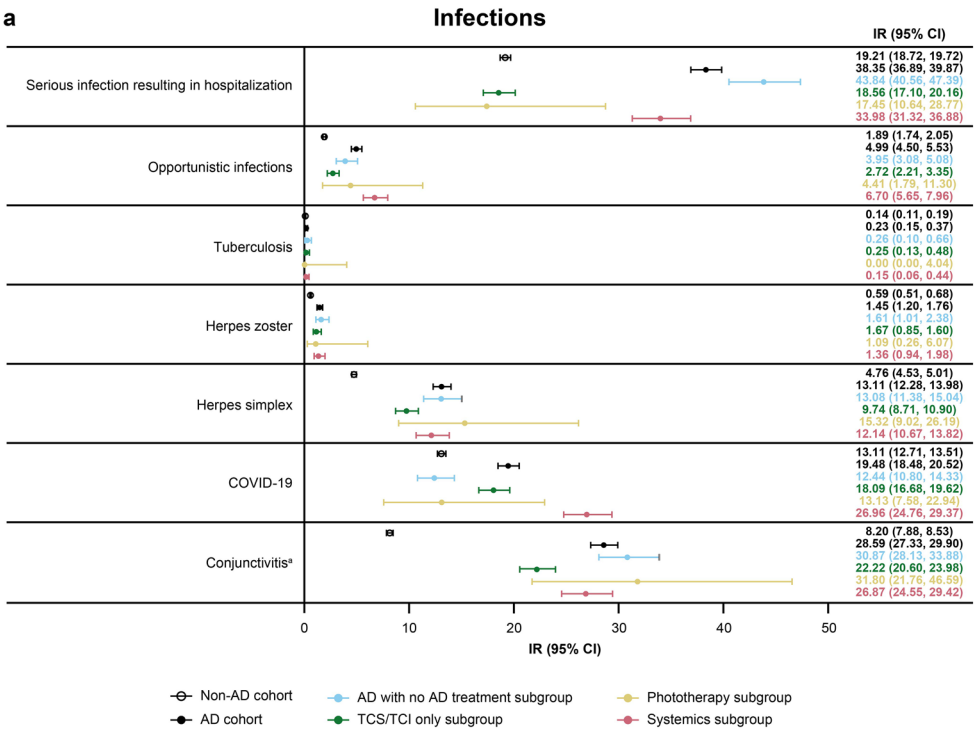
Baseline demographics and medical history	AD cohort (*n* = 26,941)	Non-AD cohort (*n* = 134,705)
Former	5000 (18.56)	21,693 (16.10)
Never	9753 (36.20)	45,628 (33.87)
Unknown	9458 (35.11)	54,577 (40.52)
Medical history,[a] *n (%)*		
Allergic rhinitis	3460 (12.84)	5249 (3.90)
Anxiety	3460 (12.84)	5249 (3.90)
Asthma	4006 (14.87)	13,902 (10.32)
Atrial fibrillation	901 (3.34)	4102 (3.05)
Congestive heart failure	886 (3.29)	3222 (2.39)
Depression	3467 (12.87)	12,269 (9.11)
Diabetes	3351 (12.44)	13,659 (10.14)
Hospitalization in last 30 days	385 (1.43)	1621 (1.20)
Hyperlipidemia	5270 (19.56)	19,645 (14.58)
Hypertension	8380 (31.11)	32,426 (24.07)
Infection in last 30 days	1827 (6.78)	5429 (4.03)
Malignancy (except NMSC)	1219 (4.52)	5516 (4.09)
Malnutrition	1196 (4.44)	3223 (2.39)
Myocardial infarction	205 (0.76)	834 (0.62)
Osteoporosis	800 (2.97)	2590 (1.92)
Stroke	412 (1.53)	1620 (1.20)

AD Atopic dermatitis, *BMI* body mass index, *EHR* electronic health records, *IQR* interquartile range, *NMSC* non-melanoma skin cancer, *SD* standard deviation

[a]Any evidence of the condition

treatment subgroups. IRs for COVID-19 were significantly higher in the systemics subgroup compared with the TCS/TCI only subgroup and phototherapy subgroup. IRs were also higher for conjunctivitis in the systemics compared with the TCS/TCI only subgroup (Fig. 2a). Crude IRs for infections stratified by baseline characteristics are presented in ESM Table S3.

In fully adjusted models, rates of all infections (except tuberculosis) were higher in the AD cohort than the non-AD cohort (Table 2). In the AD cohort, HRRs ranged from 1.33 (95% CI 1.25, 1.42; COVID-19) to 2.96 (2.78, 3.15; conjunctivitis). Rates of all infections (except tuberculosis and COVID-19) were significantly higher in the no AD treatment subgroup versus the non-AD cohort. Rates were significantly higher in the TCS/TCI only subgroup versus the non-AD cohort for herpes zoster, herpes simplex, COVID-19, and conjunctivitis, but not for serious or opportunistic infections or tuberculosis. Rates were significantly higher in the phototherapy subgroup versus the non-AD cohort for herpes simplex infection and conjunctivitis, but not for serious


a
Infections
IR (95% CI)
Serious infection resulting in hospitalization
19.21 (18.72, 19.72)
38.35 (36.89, 39.87)
43.84 (40.56, 47.38)
18.56 (17.10, 20.16)
17.45 (10.64, 28.77)
33.98 (31.32, 36.88)
Opportunistic infections
1.89 (1.74, 2.05)
4.99 (4.50, 5.53)
3.95 (3.08, 5.08)
2.72 (2.21, 3.35)
4.41 (1.79, 11.30)
6.70 (5.65, 7.96)
Tuberculosis
0.14 (0.11, 0.19)
0.23 (0.15, 0.37)
0.26 (0.10, 0.66)
0.25 (0.13, 0.48)
0.00 (0.00, 4.04)
0.15 (0.06, 0.44)
Herpes zoster
0.59 (0.51, 0.68)
1.45 (1.20, 1.76)
1.61 (1.01, 2.58)
1.67 (0.85, 1.60)
1.09 (0.26, 6.07)
1.36 (0.94, 1.98)
Herpes simplex
4.76 (4.53, 5.01)
13.11 (12.28, 13.98)
13.08 (11.38, 15.04)
9.74 (8.71, 10.90)
15.32 (9.02, 26.19)
12.14 (10.67, 13.82)
COVID-19
13.11 (12.71, 13.51)
19.48 (18.48, 20.52)
12.44 (10.80, 14.33)
18.09 (16.68, 19.62)
13.13 (7.58, 22.94)
26.96 (24.76, 29.37)
Conjunctivitis[a]
8.20 (7.88, 8.53)
28.59 (27.33, 29.90)
30.87 (28.19, 33.88)
22.22 (20.60, 23.98)
31.80 (21.76, 46.59)
26.87 (24.55, 29.42)
0
10
20
30
40
50
IR (95% CI)
Non-AD cohort
AD cohort
AD with no AD treatment subgroup
TCS/TCI only subgroup
Phototherapy subgroup
Systemics subgroup

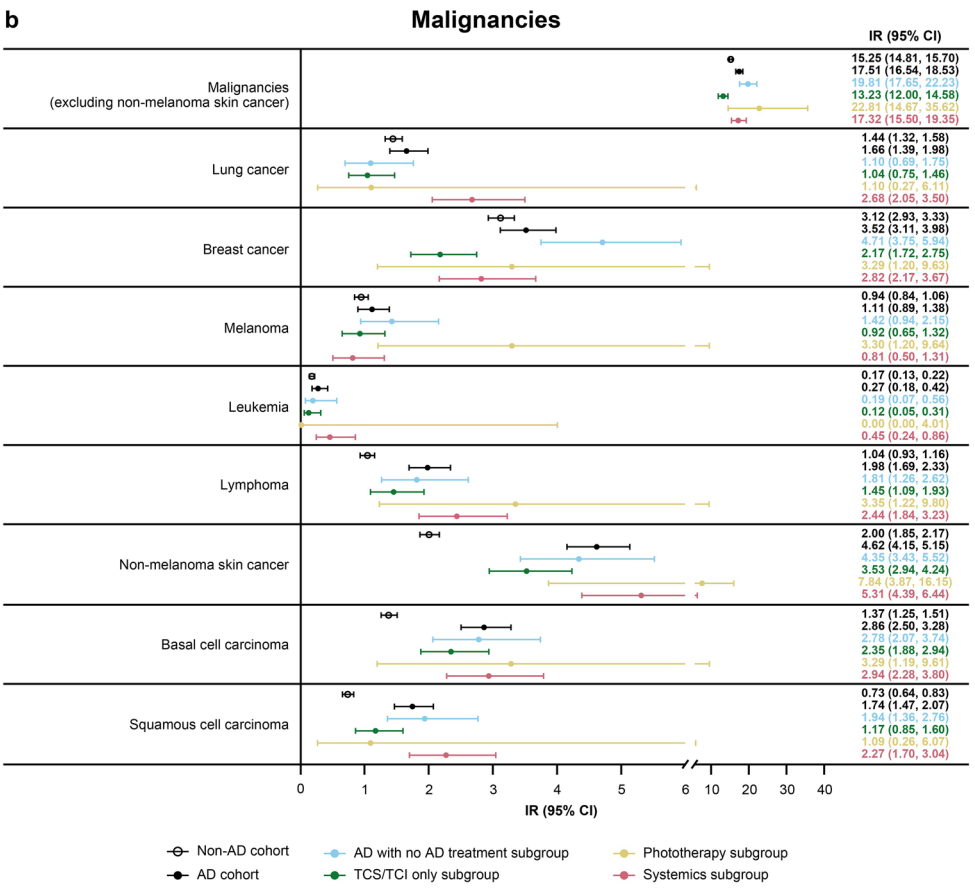

b
Malignancies
IR (95% CI)
Malignancies (excluding non-melanoma skin cancer)
15.25 (14.81, 15.70)
17.51 (16.54, 18.53)
19.81 (17.65, 22.23)
13.23 (12.00, 14.58)
22.81 (14.67, 35.62)
17.32 (15.50, 19.35)
Lung cancer
1.44 (1.32, 1.58)
1.66 (1.39, 1.98)
1.10 (0.69, 1.75)
1.04 (0.75, 1.46)
1.10 (0.27, 6.11)
2.68 (2.05, 3.50)
Breast cancer
3.12 (2.93, 3.33)
3.52 (3.11, 3.98)
4.71 (3.75, 5.94)
2.17 (1.72, 2.75)
3.29 (1.20, 9.63)
2.82 (2.17, 3.67)
Melanoma
0.94 (0.84, 1.06)
1.11 (0.89, 1.38)
1.42 (0.94, 2.15)
0.92 (0.65, 1.32)
3.30 (1.20, 9.64)
0.81 (0.50, 1.31)
Leukemia
0.17 (0.13, 0.22)
0.27 (0.18, 0.42)
0.19 (0.07, 0.56)
0.12 (0.05, 0.31)
0.00 (0.00, 4.01)
0.45 (0.24, 0.86)
Lymphoma
1.04 (0.93, 1.16)
1.98 (1.69, 2.33)
1.81 (1.26, 2.62)
1.45 (1.09, 1.93)
3.35 (1.22, 9.20)
2.44 (1.84, 3.23)
Non-melanoma skin cancer
2.00 (1.85, 2.17)
4.62 (4.15, 5.15)
4.35 (3.43, 5.52)
3.53 (2.94, 4.24)
7.84 (3.87, 16.15)
5.31 (4.39, 6.44)
Basal cell carcinoma
1.37 (1.25, 1.51)
2.86 (2.50, 3.28)
2.78 (2.07, 3.74)
2.35 (1.88, 2.94)
3.29 (1.19, 9.61)
2.94 (2.28, 3.80)
Squamous cell carcinoma
0.73 (0.64, 0.83)
1.74 (1.47, 2.07)
1.94 (1.36, 2.76)
1.17 (0.85, 1.60)
1.09 (0.26, 6.07)
2.27 (1.70, 3.04)
0
1
2
3
4
5
6
10
20
30
40
IR (95% CI)
Non-AD cohort
AD cohort
AD with no AD treatment subgroup
TCS/TCI only subgroup
Phototherapy subgroup
Systemics subgroup

Fig. 2 Crude IRs (95% CIs) per 1000 PY of select infections (**a**), malignancies (**b**), cardiovascular events (**c**), and asthma, mental health outcomes, fracture, and death events (**d**) among patients with and without AD, and by treatment subgroup. [a]May include conjunctivitis of infectious and non-infectious etiology (e.g., allergic). Systemic therapies included oral and injectable corticosteroids, immunosuppressants/immunomodulators (azathioprine, cyclosporine, interferon gamma, methotrexate, mycophenolic acid/mycophenolic mofetil), and monoclonal antibodies (dupilumab, omalizumab, rituximab). *AD* Atopic dermatitis, *CI* confidence interval, *COVID-19* coronavirus disease 2019, *IR* incidence rate, *PY* patient-years, *TCS/TCI* topical corticosteroids/topical calcineurin inhibitors

infections, opportunistic infections, herpes zoster infection, or COVID-19. Rates of all infections (except tuberculosis) were higher in the systemics subgroup than in the non-AD cohort.

Malignancies

Crude IRs were greater in the AD cohort versus the non-AD cohort for overall malignancies (excluding NMSC) and for lymphoma, NMSC, BCC, and SCC (Fig. 2b). In the AD cohort, IRs/1000 PY (95% CI) for malignancy events ranged from 0.27 (0.18, 0.42; leukemia) to 17.51 (16.54, 18.53; overall malignancies [excluding NMSC]). The IRs for overall malignancies (excluding NMSC) were significantly higher in the no AD treatment and phototherapy subgroups compared with the TCS/TCI only subgroup. The IR for lung cancer was significantly lower in the no AD treatment subgroup compared with the systemics group. The IR for breast cancer was significantly higher in the no AD treatment subgroup compared with the TCS/TCI only and systemics subgroups. The IRs for overall malignancy (excluding NMSC) and for lung cancer, NMSC, and SCC events were significantly higher in the systemics subgroup compared with the TCS/TCI only subgroup. Crude IRs for malignancies stratified by baseline characteristics are presented in ESM Table S4.

In fully adjusted models, rates of overall malignancies (excluding NMSC) and breast cancer were 18% higher in the AD cohort versus the non-AD cohort, while rates of lymphoma, NMSC, BCC, and SCC were approximately twofold higher in the AD versus non-AD cohort (Table 2). Rates were significantly higher in the no AD treatment subgroup versus the non-AD cohort for overall malignancies (excluding NMSC), breast cancer, lymphoma, NMSC, BCC, and SCC. Rates were 26% lower for breast cancer and approximately 50–90% higher for lymphoma, NMSC, BCC, and SCC in the TCS/TCI only subgroup versus the non-AD subgroup. Rates of melanoma, lymphoma, and NMSC were more than threefold higher in the phototherapy subgroup than in the non-AD cohort; however, the 95% CIs were wide due to low patient numbers in these subgroups. Rates were significantly higher in the systemics subgroup versus the non-AD cohort for lung cancer, leukemia, lymphoma, NMSC, BCC, and SCC.

Cardiovascular Events

Crude IRs were greater in the AD cohort versus the non-AD cohort for all cardiovascular events. The IRs/1000 PY (95% CI) for CV outcomes ranged from 4.20 (3.75, 4.70) for PE to 16.51 (15.59, 17.49) for MACE. The IRs for MACE, MI, stroke, peripheral artery disease (PAD), and DVT were significantly higher in the no AD treatment subgroup compared with the TCS/TCI only subgroup. The IR for VTE was significantly higher in the systemics subgroup compared with the no AD treatment subgroup, and IRs for all cardiovascular events were significantly higher in the systemics subgroup compared with the TCS/TCI only subgroup (Fig. 2c). Crude IRs for cardiovascular events stratified by baseline characteristics are presented in ESM Table S5.

In fully adjusted models, the rates of all cardiovascular events were significantly greater in the AD versus non-AD cohort (Table 2). In the AD cohort, HRRs (95% CI) ranged from 1.18 (1.09, 1.29; stroke) to 1.53 (1.41, 1.67; VTE). Rates of all cardiovascular events (except PE) were significantly higher in the no AD treatment subgroup versus the non-AD cohort. Rates were higher for VTE (1.14 [CI, 1.00, 1.30]) and lower for stroke (0.85 [0.74, 0.98]) in the TCS/TCI only subgroup versus the non-AD cohort. Rates of cardiovascular events in the phototherapy subgroup were not statistically significantly different from the non-AD cohort. Rates were higher for all

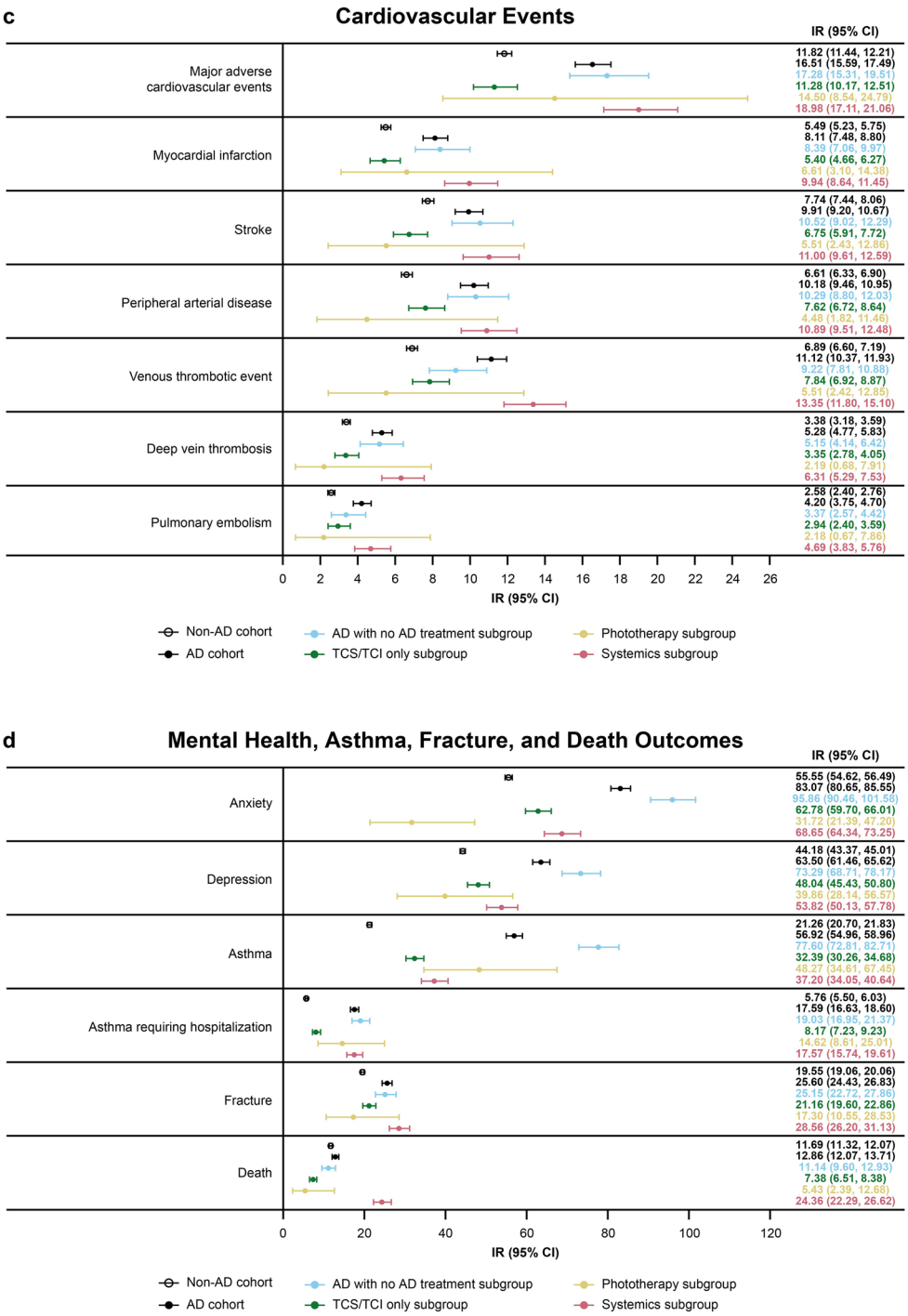


Fig. 2 continued

Table 2 Fully adjusted hazard rate ratios of select disease events among patients with atopic dermatitis compared with patients without atopic dermatitis, stratified by treatment the Optum® electronic health records database (2016–2021)

Select disease events	HRRs (95% CI)									
	AD cohort ($n = 26,941$)	*P* value	No AD treatment ($n = 8384$)	*P* value	TCS/TCI only ($n = 13,459$)	*P* value	Phototherapy with/without TCS/TCI, without systemics ($n = 366$)	*P* value	Systemics with/without TCS/TCI, with/without phototherapy ($n = 3706$)	*P* value
Infections										
Serious infections[a]	1.88 (1.79, 1.97)	< 0.01	2.26 (2.08, 2.46)	< 0.01	0.93 (0.85, 1.02)	0.10	0.83 (0.50, 1.38)	0.46	1.43 (1.31, 1.57)	< 0.01
Opportunistic infections[a]	2.14 (1.87, 2.46)	< 0.01	1.91 (1.46, 2.49)	< 0.01	1.23 (0.98, 1.55)	0.08	1.99 (0.74, 5.35)	0.17	2.27 (1.84, 2.81)	< 0.01
Tuberculosis[a,b]	1.46 (0.82, 2.61)	0.20	1.54 (0.55, 4.32)	0.42	1.37 (0.63, 2.97)	0.42	No Convergence	N/A	0.79 (0.23, 2.66)	0.70
Herpes zoster[a]	2.11 (1.64, 2.71)	< 0.01	2.57 (1.68, 3.92)	< 0.01	1.79 (1.25, 2.56)	< 0.01	1.55 (0.22, 11.12)	0.66	1.72 (1.11, 2.66)	0.01
Herpes simplex[a]	2.65 (2.43, 2.89)	< 0.01	2.61 (2.24, 3.04)	< 0.01	1.84 (1.62, 2.09)	< 0.01	3.23 (1.87, 5.60)	< 0.01	2.32 (2.00, 2.70)	< 0.01
COVID-19[a]	1.33 (1.25, 1.42)	< 0.01	1.04 (0.89, 1.20)	0.64	1.41 (1.29, 1.54)	< 0.01	0.90 (0.51, 1.59)	0.72	2.03 (1.84, 2.24)	< 0.01
Conjunctivitis[a,c]	2.96 (2.78, 3.15)	< 0.01	3.29 (2.96, 3.64)	< 0.01	2.23 (2.04, 2.44)	< 0.01	3.42 (2.32, 5.05)	< 0.01	2.52 (2.26, 2.81)	< 0.01
Malignancies										
Malignancy excl NMSC[d]	1.18 (1.11, 1.26)	< 0.01	1.28 (1.13, 1.44)	< 0.01	0.92 (0.83, 1.02)	0.12	1.54 (0.98, 2.42)	0.06	1.07 (0.96, 1.20)	0.23
Lung cancer[d]	1.16 (0.95, 1.42)	0.15	0.76 (0.47, 1.24)	0.27	0.78 (0.55, 1.11)	0.17	0.76 (0.11, 5.41)	0.78	1.70 (1.27, 2.26)	< 0.01
Breast cancer[d]	1.18 (1.03, 1.36)	0.02	1.48 (1.16, 1.88)	0.01	0.74 (0.58, 0.95)	0.02	1.33 (0.43, 4.14)	0.62	0.83 (0.63, 1.10)	0.19
Melanoma[d,e]	1.20 (0.94, 1.54)	0.14	1.47 (0.95, 2.26)	0.08	1.02 (0.70, 1.48)	0.93	3.35 (1.07, 10.47)	0.04	0.80 (0.48, 1.33)	0.39
Leukemia[d]	1.54 (0.92, 2.59)	0.10	1.13 (0.35, 3.63)	0.84	0.76 (0.27, 2.11)	0.60	No Convergence	N/A	2.43 (1.19, 4.98)	0.02
Lymphoma[d]	1.99 (1.63, 2.42)	< 0.01	1.72 (1.17, 2.53)	0.01	1.51 (1.11, 2.06)	0.01	3.12 (1.00, 9.74)	0.05	2.29 (1.69, 3.11)	< 0.01
NMSC[d,e]	2.34 (2.04, 2.67)	< 0.01	2.18 (1.69, 2.80)	< 0.01	1.89 (1.54, 2.30)	< 0.01	3.81 (1.81, 8.03)	< 0.01	2.49 (2.02, 3.07)	< 0.01
BCC[d,e]	2.14 (1.81, 2.52)	< 0.01	2.02 (1.48, 2.77)	< 0.01	1.83 (1.43, 2.34)	< 0.01	2.37 (0.76, 7.39)	0.14	2.03 (1.54, 2.68)	< 0.01

Table 2 continued

Select disease events	HRRs (95% CI)									
	AD cohort ($n = 26{,}941$)	*P* value	No AD treatment ($n = 8384$)	*P* value	TCS/TCI only ($n = 13{,}459$)	*P* value	Phototherapy with/without TCS/TCI, without systemics ($n = 366$)	*P* value	Systemics with/without TCS/TCI, with/without phototherapy ($n = 3706$)	*P* value
SCC[d,e]	2.33 (1.88, 2.90)	< 0.01	2.66 (1.82, 3.90)	< 0.01	1.67 (1.19, 2.36)	0.03	1.35 (0.19, 9.64)	0.76	2.84 (2.06, 3.93)	< 0.01
Cardiovascular events										
MACE[f]	1.31 (1.22, 1.40)	< 0.01	1.40 (1.23, 1.59)	< 0.01	0.93 (0.83, 1.04)	0.20	1.13 (0.65, 1.95)	0.67	1.37 (1.22, 1.53)	< 0.01
MI[f]	1.37 (1.24, 1.51)	< 0.01	1.48 (1.24, 1.78)	< 0.01	0.97 (0.82, 1.13)	0.66	1.13 (0.51, 2.53)	0.76	1.50 (1.28, 1.75)	< 0.01
Stroke[f]	1.18 (1.09, 1.29)	< 0.01	1.28 (1.09, 1.50)	0.03	0.85 (0.74, 0.98)	0.02	0.65 (0.27, 1.55)	0.33	1.18 (1.02, 1.36)	0.03
Peripheral arterial disease[f]	1.42 (1.30, 1.55)	< 0.01	1.47 (1.25, 1.74)	< 0.01	1.11 (0.97, 1.27)	0.12	0.65 (0.24, 1.73)	0.39	1.35 (1.16, 1.56)	< 0.01
VTE[g]	1.53 (1.41, 1.67)	< 0.01	1.32 (1.11, 1.57)	0.01	1.14 (1.00, 1.30)	0.05	0.74 (0.31, 1.77)	0.49	1.63 (1.43, 1.87)	< 0.01
DVT[g]	1.50 (1.33, 1.69)	< 0.01	1.50 (1.19, 1.89)	0.01	0.98 (0.80, 1.19)	0.83	0.60 (0.15, 2.39)	0.47	1.57 (1.30, 1.90)	< 0.01
PE[g]	1.51 (1.32, 1.72)	< 0.01	1.30 (0.98, 1.72)	0.07	1.14 (0.92, 1.42)	0.22	0.77 (0.19, 3.10)	0.71	1.49 (1.20, 1.86)	< 0.01
Mental health outcomes										
Anxiety[h]	1.57 (1.51, 1.62)	< 0.01	1.72 (1.62, 1.83)	< 0.01	1.13 (1.08, 1.20)	< 0.01	0.61 (0.41, 0.92)	0.02	1.23 (1.15, 1.32)	< 0.01
Depression[h]	1.49 (1.43, 1.55)	< 0.01	1.64 (1.54, 1.76)	< 0.01	1.08 (1.01, 1.14)	0.02	0.95 (0.67 1.35)	0.76	1.18 (1.09, 1.27)	< 0.01
Other										
Asthma[i]	2.65 (2.54, 2.77)	< 0.01	3.30 (3.08, 3.54)	< 0.01	1.37 (1.27, 1.47)	< 0.01	2.18 (1.55, 3.05)	< 0.01	1.59 (1.45, 1.75)	< 0.01
Asthma resulting in hospitalization[i]	2.78 (2.58, 3.00)	< 0.01	3.08 (2.71, 3.50)	< 0.01	1.20 (1.05, 1.37)	0.01	2.29 (1.32, 3.95)	< 0.01	2.41 (2.13, 2.73)	< 0.01
Fracture[j]	1.27 (1.20, 1.34)	< 0.01	1.30 (1.17, 1.44)	< 0.01	1.09 (1.01, 1.19)	0.03	0.88 (0.53, 1.45)	0.61	1.25 (1.14, 1.37)	< 0.01
Death[k]	1.08 (1.00, 1.16)	0.04	0.97 (0.84, 1.14)	0.75	0.68 (0.60, 0.78)	< 0.01	0.48 (0.2, 1.16)	0.10	1.88 (1.71, 2.07)	< 0.01

Table 2 continued

Systemic therapies included oral and injectable corticosteroids, immunosuppressants/immunomodulators (azathioprine, cyclosporine, interferon gamma, methotrexate, mycophenolic acid/mycophenolic mofetil), and monoclonal antibodies (dupilumab, omalizumab, rituximab)

P values were generated via multivariable Cox regression models

AD Atopic dermatitis, *BCC* basal cell carcinoma, *BMI* body mass index, *CI* confidence interval, *COVID-19* coronavirus disease-2019, *DVT* deep vein thrombosis, *HRR* hazard rate ratio, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *N/A* not applicable, *NMSC* non-melanoma skin cancer, *PE* pulmonary embolism, *SCC* squamous cell carcinoma, *TCS/TCI* topical corticosteroids/topical calcineurin inhibitors, *VTE* venous thromboembolism

[a]Variables included in the model: age, sex, race, BMI, smoking status, history of allergic rhinitis, history of asthma, history of congestive heart failure, history of chronic kidney disease, history of chronic obstructive pulmonary disease, history of dementia, history of depression, history of diabetes, history of inflammatory bowel disorder, history of liver disease, history of infection in last 30 days, history of hospitalization in last 30 days, history of systemic steroids in last 90 days, and history of inhaled steroids in last 90 days

[b]History of dementia was removed from model because it did not converge

[c]May include conjunctivitis of infectious and non-infectious etiology (e.g., allergic)

[d]Variables included in the model: age, sex, race, BMI, and smoking status

[e]Race was removed from model because it did not converge

[f]Variables included in the MACE, MI, stroke, and peripheral arterial disease models: age, sex, race, BMI, smoking status, history of diabetes, history of hypertension, history of hyperlipidemia, history of chronic kidney disease, history of depression, history of anxiety, history of allergic rhinitis, history of asthma, and history of systemic steroids in last 90 days

[g]Variables included in the DVT, VTE, and PE models: age, sex, race, BMI, smoking status, history of malignancy, history of congestive heart failure, history of respiratory failure, history of pregnancy, history of oral contraceptive pill/hormone replacement use, history of chronic kidney disease, history of MI, history of atrial fibrillation, history of diabetes, history of hypertension, history of chronic obstructive pulmonary disease, and history of liver disease

[h]Variables included in the anxiety and depression models: age, sex, race, BMI, smoking status, history of allergic rhinitis, and history of asthma

[i]Variables included in the asthma models: age, sex, race, BMI, smoking status, and history of allergic rhinitis

[j]Variables included in the fracture model: age, sex, race, BMI, smoking status, history of antidepressant use, history of antiepileptic use, history of atrial fibrillation, history of chronic heart failure, history of chronic obstructive pulmonary disease, history of systemic steroid use in last 90 days, history of dementia, history of diabetes, history of hormone therapy, history of hyperthyroidism, history of liver disease, history of malignancy excluding NMSC, history of malnutrition, history of osteoporosis, history of proton pump inhibitor use, and history of stroke

[k]Variables included in the death model: age, sex, race, BMI, and smoking status

cardiovascular events in the systemics subgroup versus the non-AD cohort; the increase ranged from 35% (PAD) to 63% (VTE).

Other Disease Events

Mental health outcomes Crude IRs for anxiety and depression were higher in the AD cohort and TCS/TCI only and systemics subgroups than in the non-AD cohort (Fig. 2D). In the AD cohort, IRs/1000 PY (95% CI) were 83.07 (80.65, 85.55) for anxiety and 63.50 (61.46, 65.62) for depression. The IRs for anxiety and depression were significantly higher in the no AD treatment group compared with the AD treatment subgroups. The IR for anxiety was significantly higher in the TCS/TCI only group compared with the phototherapy group, and the IR for anxiety was significantly higher in the systemics subgroup compared with the phototherapy subgroup. Crude IRs for mental health outcomes stratified by baseline characteristics are presented in ESM Table S6.

In fully adjusted analyses, rates were significantly higher in the AD cohort versus the non-AD cohort for anxiety (HRR 1.57 [95% CI 1.51, 1.62]) and depression (1.49 [1.43, 1.55]; Table 2). Increased rates were also observed for the no AD treatment, TCS/TCI only, and systemics subgroups versus the non-AD cohort. The rate of anxiety was lower in the phototherapy subgroup versus the non-AD cohort, while the rate of depression was not significantly different between these groups.

Asthma Crude IRs for asthma and asthma resulting in hospitalization were 2.7-fold and threefold higher in the AD versus non-AD cohort, respectively (Fig. 2d). In the AD cohort, IRs/1000 PY (95% CI) for asthma and asthma resulting in hospitalization were 56.92 (54.96, 58.96) and 17.59 (16.63, 18.60), respectively. The IR for asthma resulting in hospitalization was significantly higher in the systemics subgroup than in the TCS/TCI only subgroup. The IR for asthma was significantly higher in the no AD treatment group compared to the AD treatment subgroups; the IR for asthma resulting in hospitalization was also higher in the no AD treatment group than in the TCS/TCI only subgroup. Crude IRs for asthma and asthma resulting in hospitalization stratified by baseline characteristics are presented in ESM Table S6.

Adjusted rates of asthma and asthma resulting in hospitalization were more than 2.5-fold higher in the AD versus non-AD cohort (Table 2). Rates were also significantly higher in the no AD treatment, TCS/TCI only, phototherapy, and systemics subgroups versus the non-AD cohort.

Fractures Crude rates of fracture were significantly higher for the AD cohort and systemics subgroup versus the non-AD cohort (Fig. 2d). In the AD cohort, the IR/1000 PY (95% CI) for fracture was 25.60 (24.43, 26.83). The IR for fracture was significantly higher in the systemics subgroup compared with the TCS/TCI only subgroup. Crude IRs for fracture stratified by baseline characteristics are presented in ESM Table S6.

In fully adjusted analyses, rates of fracture were ≥ 25% higher in the AD cohort and no AD treatment and systemics subgroups and approximately 9% higher in the TCS/TCI only subgroup compared with the non-AD cohort (Table 2). The rate of fracture was not significantly different in the phototherapy subgroup versus the non-AD cohort.

Death Crude rates (95% CI) of death were comparable between the AD (12.86 [12.07, 13.71]) and non-AD cohorts (11.69 [11.32, 12.07]; Fig. 2D). IRs for death were significantly higher in the systemics subgroup compared with the no AD treatment cohort, TCS/TCI only subgroup, and phototherapy subgroup. The IR for death was also significantly higher in the no AD treatment group compared with the TCS/TCI only subgroup.

In fully adjusted analyses, the rate of death was 8% higher in the AD cohort, 32% lower in the TCS/TCI only subgroup, and 88% higher in the systemics subgroup versus the non-AD cohort (Table 2). The rate of death was not significantly different in the no AD treatment and phototherapy subgroups versus the non-AD cohort.

DISCUSSION

This large retrospective cohort study of EHR data from the US-based Optum® Market Clarity database examined rates of select disease events in patients with and without AD, identified based on previously reported associations and recommendations from key opinion leaders. The rates of several disease events were higher in patients with AD versus those without AD, similar to results from previous studies which identified positive associations between AD and select disease events. Crude IRs for several disease events were higher in the systemics subgroup versus the TCS/TCI only subgroup; of note, data collection occurred prior to the introduction of systemic Janus kinase (JAK) inhibitors for the treatment of AD. Our findings complement recent UK, US, and Taiwan cohort-based studies of EHR and claims data [15, 18–20, 21–25, 29, 33], which is reassuring given the inherent differences in data captured by claims (i.e., coverage decisions, resource utilization) and EHR databases (i.e., clinical decisions, practice notes, and geographic variation in coverage) [34]. Although phototherapy is not commonly prescribed for AD, we included a phototherapy subgroup in our analyses as it was recommended as a second-line treatment by relevant clinical guidelines at the time of the study [33]. A no AD treatment subgroup was included as a proxy for patients with mild AD. Surprisingly, rates of many disease events were higher in this subgroup compared with the non-AD cohort, suggesting that the no AD treatment subgroup may have included patients with uncontrolled AD of any severity level. As such, underlying comorbid conditions or prescribed treatments unrelated to AD may have contributed to higher rates of some disease events.

The risk of pneumonia, herpes simplex, and serious, and opportunistic infections was found to be higher in patients with AD versus the general UK population in previous cohort studies [11, 21], and the risk of COVID-19, conjunctivitis, and allergic conjunctivitis was found to be higher in patients with AD versus the general US population [22, 31, 32]. Although the rate of COVID-19 was assessed in the current study, COVID-19 vaccination status was not examined. In the current analysis, rates of infections were between 33% (COVID-19) and 196% (conjunctivitis) higher in the AD cohort versus the non-AD cohort, which could be attributable in part to the use of systemic therapies, which have previously been shown to increase the risk of infection and malignancies [33]. Indeed, in the current study, the rates of most infections were higher in the systemics subgroup versus the TCS/TCI only subgroup. However, as adjusted rates were also significantly greater in the TCS/TCI only subgroup versus the non-AD cohort for herpes zoster, herpes simplex, COVID-19, and conjunctivitis, the increased risk of infection in patients with AD may not be fully attributable to treatment type, and underlying disease pathogenesis may contribute to the risk of infection [36]. These findings are in line with those from previous UK-based cohort studies, which, alongside the impact of systemic therapy, highlighted the contribution of skin barrier defects and immune dysregulation to the increased risk of infection in patients with AD [11, 21].

In the current study, rates of overall malignancy (excluding NMSC), breast cancer, lymphoma, NMSC, BCC, and SCC were significantly higher in patients with AD versus patients without AD, reflecting the results of previous EHR and claims database studies conducted in the UK, Denmark, and Taiwan [19, 20, 29, 37]. In the UK, severe AD was associated with a threefold higher risk of lymphoma in adults and children with severe AD [2]. Although the pathophysiology underlying the association between AD and malignancy is unclear, immune dysfunction and chronic inflammation may contribute to the increased risk of solid organ tumors (i.e., breast cancer) in patients with AD [38, 39]. Increased skin surveillance resulting from long-term clinical monitoring may lead to greater detection of skin cancers (i.e., NMSC, BCC and SCC) in patients with AD [40]. Future studies are warranted to further elucidate the relationship between AD and malignancies.

The risk of cardiovascular events, including angina pectoris, MI, stroke, VTE, DVT, and cardiovascular death was increased in patients with AD versus demographically- and index-matched

controls in Denmark, UK, Taiwan, and South Korea [13, 23–25]. This result is consistent with that of the present study wherein rates of all evaluated cardiovascular events were significantly higher in patients with AD versus patients without AD. As chronic systemic inflammation is common to the pathophysiology of both AD and cardiovascular disease, this factor likely contributes to the increased risk of cardiovascular events in patients with AD [41].

Similar to the current study, AD was associated with depression and anxiety in a global systematic review and meta-analysis [42], and a longitudinal study using Taiwanese claims data identified an increased risk of depression and anxiety outcomes in patients with AD versus patients without AD [43]. Furthermore, consistent with the current study, increased risks of low bone mineral density, osteopenia, osteoporosis, and related fractures in patients with AD versus patients without AD were reported in a systematic review and meta-analysis [45], which may be partly attributable to the use of systemic and topical corticosteroids [46]. Taiwan and UK population-based cohort studies have also reported that exposure to systemic corticosteroids was associated with an increased risk of fracture [34, 47].

A UK population-based cohort study reported a 4% higher risk of all-cause mortality in patients with AD versus patients without AD; however, the mortality risk was 60% higher in patients with severe AD compared with the non-AD controls, primarily due to infection and respiratory disease [47]. This is consistent with the current analysis wherein the adjusted mortality rate was 8% higher in patients with AD versus patients without AD, and 88% higher in the systemics subgroup, possibly reflecting patients with more severe disease.

Some studies have reported little to no impact of AD on the risk of select disease events, including many types of malignancies, VTE, DVT, and PE [14, 19]. This may be due to differing ICD codes used to define AD and disease events of interest. Additionally, some studies may have excluded patients with a history of comorbidities [13–16, 18–21, 23–25, 29, 34, 44], resulting in healthier baseline study populations.

Limitations

Previous insurance claims and EHR database studies have demonstrated poor predictive value of using ICD codes to identify AD, resulting in potential misclassification [48–50]. To minimize misclassification, we used ≥ 1 inpatient or ≥ 2 outpatient codes to identify patients with AD. Although previous studies have indicated that the positive predictive values of ICD codes for AD are increased when used concomitantly with codes for comorbid allergic conditions [48], this approach was not used in the current study. Misclassification of disease events was possible, and causality could not be inferred from these observational analyses. In addition, AD diagnosis prior to the study period was unknown, and the follow-up time may have been insufficient to capture rates of events with longer induction or latency periods. The use of the Optum® EHR database may have resulted in overrepresentation of patients aged ≥ 65 years (24%) and from the Midwest USA (51%). As patients with AD are more likely to visit a dermatologist and undergo close monitoring of the skin than patients without AD, these findings are subject to potential ascertainment and surveillance bias, particularly for skin cancer outcomes.

Although AD severity was not directly captured in this study, analyses were stratified by treatment subgroups, which may serve as a proxy for disease severity and is a common approach in many EHR- and claims-based studies [13–16, 18, 21, 23–25, 28, 33, 45, 46]. Although claims data served as proxies for AD treatment, it was not possible to verify treatment usage, and over-the-counter corticosteroid use could not be captured. In addition, these analyses did not address dosage and duration or the underlying reason for prescription, and therapies may have been prescribed off-label. Treatments may have been used for indications other than AD, potentially impacting our subgroup classification. Treatment use could itself have contributed to associations between AD and select disease events. Individual drugs within each subgroup may have different associations with each disease event. Patients with AD who

received treatment for more advanced disease (e.g., systemics) may have received simultaneous treatment with phototherapy and TCS/TCI; however, associations between concurrent therapy use and disease events were not specifically examined.

Statistical adjustment controlled for known confounding variables; however, unknown confounders could not be considered. As this was an exploratory study, statistical adjustment for multiple comparisons was not made, which might have inflated the Type I error rate. Factors which may have contributed to inconsistent effect sizes and direction across categories included small sample sizes for certain disease events (e.g., tuberculosis) and treatment subgroups (e.g., phototherapy), variability in recording at the point of care, and record keeping problems inherent to all real-world data; results should be interpreted with caution. Although data were included from a large number of patients (26,941 and 134,705 in the AD cohort and non-AD cohort, respectively), repeated data binning and the rare nature of some disease events led to low event frequencies for some analyses in this study. Finally, these data may not be generalizable to the entire US population as the Optum® EHR database does not capture untreated individuals.

Conclusions

In this retrospective observational analysis of US EHR data rates of certain disease events were higher in patients with AD versus patients without AD. Rates of select disease events were generally highest in patients receiving systemic therapies and not as high in patients using only TCS/TCIs. The current study further informs the incidence of select disease events in patients with AD and may aid clinicians in predicting event risk and how AD treatments may influence these frequencies. These data may also help contextualize the safety profile of AD therapies in clinical trials.

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Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified patient data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declarations

Conflict of Interest. *Alexander Egeberg* is currently employed by LEO Pharma and has previously received research funding from Pfizer Inc., AbbVie, Almirall, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly and Company, Novartis, Janssen, the Danish National Psoriasis Foundation, the Simon Spies Foundation, and the Kgl Hofbundtmager Aage Bang Foundation; and honoraria as consultant and/or speaker

from Pfizer Inc., AbbVie, Amgen, Almirall, Bristol-Myers Squibb, Boehringer Ingelheim, Dermavant, Eli Lilly and Company, Galápagos NV, Galderma, Horizon Therapeutics, Janssen, LEO Pharma, McNeil Consumer Healthcare, Mylan, Novartis, Samsung Bioepis Co., Ltd., Sun Pharmaceuticals, UCB, Union Therapeutics, and Zuellig Pharma Ltd. *Thomas Edwards* is an employee of Panalgo and received consultancy fees from Pfizer Inc. *Jonathan I Silverberg* has served as an investigator for Celgene, Eli Lilly and Company, F. Hoffmann-La Roche, Menlo Therapeutics, Realm Therapeutics, Regeneron Pharmaceuticals, and Sanofi Genzyme; as a consultant for Pfizer Inc., AbbVie, Anacor, AnaptysBio, Arena Pharmaceuticals, Dermavant, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Glenmark, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, Menlo Therapeutics, Novartis, Realm Therapeutics, Regeneron Pharmaceuticals, and Sanofi Genzyme; and as a speaker for Regeneron Pharmaceuticals and Sanofi Genzyme. *Stephen E Schachterle*, *Daniela E Myers*, and *Adina R Lemeshow* are employees and shareholders of Pfizer Inc. *William Romero* is currently employed by Eli Lilly and Company and was an employee and shareholder of Pfizer Inc. at the time of the study. *Shefali Vyas* is currently employed by AstraZeneca and was an employee and shareholder of Pfizer Inc. at the time of the study.

Ethical Approval. This was a retrospective database study and was not subject to ethical review.

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