Title

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Risk of herpesvirus, serious and opportunistic infections in atopic dermatitis: a population-based cohort study

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Summary

Background—Staphylococcal and herpes simplex virus (HSV) infections are commonly recognized in atopic dermatitis (AD), but less is known about other types of infections.

Objectives—To determine the risk of herpesvirus infections, serious infections and opportunistic infections in patients with AD.

Methods—We conducted a population-based cohort study using UK-based electronic medical records data. Patients with AD were each matched to up to five unaffected patients on age, practice and index date. AD severity was defined using treatments as a proxy. Outcomes were incident herpesvirus infections [cytomegalovirus (CMV), Epstein–Barr virus (EBV), HSV or varicella zoster virus (VZV)], serious infections and opportunistic infections.

Results—Among 409 431 children and 625 083 adults with AD matched to 1 809 029 children and 2 678 888 adults without AD, respectively, adjusted Cox regression models showed children and adults with AD had a 50–52% greater risk of HSV and 18–33% greater risk of VZV, with risk increasing in parallel with AD severity. CMV risk was elevated among children with AD [hazard ratio (HR) 2·50, 95% confidence interval (95% CI) 1·38–4·54] and adults with severe AD (HR 4·45, 95% CI 1·76–11·25). Patients with AD had a 26–40% increase in risk of serious infections, with severe AD carrying the greatest risk. Although rare, opportunistic infections were associated with all severities of AD in adults (overall HR 1·31, 95% CI 1·20–1·42), but were not associated with AD in children. All estimates remained consistent after excluding patients receiving immunosuppressive treatments for AD.

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Conclusions—AD is significantly associated with herpesvirus infections, serious infections and opportunistic infections in a ‘dose-dependent’ manner with increasing severity. AD may increase susceptibility to infections exclusive of immunosuppressive medications.

Atopic dermatitis (AD) is associated with epidermal barrier defects, decreased antimicrobial peptide expression and altered innate and adaptive immunity in the setting of T-helper (Th) 2-skewed inflammation, which can increase susceptibility to infections.[1,2] Staphylococcal and herpes simplex virus (HSV) infections are commonly recognized infections in AD.[3] Eczema herpeticum (EH), a disseminated cutaneous HSV infection linked to defective interferon response and cathelicidin deficiency, is uncommon but may be more prevalent in moderate-to-severe AD.[4–6] Patients with AD may also be at greater risk for extracutaneous infections, such as respiratory, gastrointestinal and urinary tract infections, owing to systemic immune dysregulation due to AD and/or its treatment.[7–10] However, previous studies of infections in AD are primarily cross-sectional and have not examined the influence of AD severity on infection risk.[7,8] Additionally, the risk of serious (i.e. hospitalized) and opportunistic infections has not been fully characterized. Although cutaneous HSV infections are widely recognized in patients with AD, few epidemiological investigations of HSV in AD exist.[11] Some studies have suggested greater rates of varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV) infections among patients with AD,[7,8,12–15] but the incidence of these other herpesvirus infections in AD remains unknown. Thus, we sought to determine the risk of herpesvirus infections, serious infections and opportunistic infections among patients with AD.

Materials and methods

We conducted a retrospective cohort study using The Health Improvement Network® (THIN®) (the-health-improvement-network.com/), a general practice medical records database in the UK. THIN is broadly representative of the UK population. General practitioners (GPs) are the primary contact for medical care in the UK, and THIN is an appropriate and validated data source for studying AD and many outcomes including infections.[16,17] Data were collected from 1994 to February 2015.

The study included all patients with AD, each matched to up to five unaffected controls (patients without AD, comprising the non-AD group) on age (+/−3 years), practice, and an encounter within +/−6 months of the index date for the patient with AD (defined as the later of practice registration and diagnosis dates). Analyses were stratified into paediatric cohorts (< 18 years old at baseline) and adult cohorts (≥18 years old). Patients with AD were identified using the presence of at least one of five common diagnosis codes for AD and two AD-related therapy codes: specifically validated for THIN, this algorithm has a positive predictive value of 86% for physician-confirmed diagnosis of AD and overcomes limitations of previous studies that used similar diagnosis code-based approaches but that lacked validation.[9,16] Matched controls were assigned a ‘diagnosis date’ based on an encounter within +/−6 months of the patient’s index date to ensure that exposed and unexposed participants were followed by similar providers during similar time periods. Follow-up time began at the latest of first AD diagnosis (or ‘diagnosis date’ for unexposed), practice registration date, or Vision date (i.e. when Vision software was implemented for THIN data,

providing data quality assurance). Follow-up ended at the earliest of outcome, transfer out of the practice, practice withdrawal from THIN, death or end of study period. Patients with history of an outcome of interest at cohort entry were excluded from the corresponding analyses.

As AD severity is not directly captured in medical record databases such as THIN, we used treatment as a proxy for severity as has been used in other epidemiological studies of AD.[18,19] All patients with AD were categorized as having mild disease by default. They were classified as having moderate AD at the first of (i) prescription for a second potent topical corticosteroid within 1 year or (ii) prescription for first topical calcineurin inhibitor (reserved for moderate AD in the UK).[20] Patients were classified as having severe AD at the first of (i) prescription for a systemic immunosuppressant, (ii) phototherapy or (iii) referral to dermatology (as 96% of patients with AD are managed exclusively by GPs).[21] 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 until end of follow-up. Although misclassification of AD severity is possible, this approach has been used in previous research and leads to severity estimates consistent with the literature.[18,19]

The primary outcomes were herpesvirus infections (CMV, EBV, HSV, VZV), hospitalized infections and opportunistic infections, identified using Read diagnosis codes. Among the HSV codes, EH was defined by specific codes for EH while the remainder were taken to signify non-EH forms of HSV. Serious infection was defined by at least one code for a pre-specified set of infections (including infections of the respiratory tract, urinary tract, gastrointestinal tract/abdominal cavity, bone or joints, central nervous system or meninges, heart, skin or soft tissue and eyes; abscesses; and sepsis) and hospitalization within 30 days, as used in previous THIN studies.[22] Opportunistic infection was defined by one or more diagnosis codes for actinomycosis/nocardiosis, aspergillosis, BK virus, cryptococcosis, cytomegalovirus, mucormycosis, other mycoses (blastomycosis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis), pneumocystis, progressive multifocal leukoencephalopathy, tuberculosis and toxoplasmosis.[22] Patients with history of malignancy, human immunodeficiency virus or organ transplantation were excluded.

AD severity and age were treated as time-updated covariates while other covariates were defined at cohort entry. Cox regression modelling was performed to compare the risk of outcomes between AD and non-AD groups, adjusted for potential confounders determined a priori, including age, sex, socioeconomic status, body mass index (BMI), smoking and drinking status, comorbidities that may impact infection risk (including asthma, allergic rhinitis, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, inflammatory bowel disease and liver disease), and vaccination history (specifically influenza, meningococcus and pneumococcus vaccines, which are routinely administered in the UK). BMI data for children were sparse, precluding their use. Sensitivity analyses were conducted to address potential biases introduced by treatments, presence of other atopic comorbidities, short study follow-up duration and ascertainment bias. As our approach to defining AD severity precludes the separation of severity vs. treatment effects, we conducted a sensitivity analysis excluding patients who received

systemic immunosuppressants. The University of Pennsylvania Institutional Review Board approved the study.

Results

Paediatric cohort

A total of 409 431 patients with AD (93·2% mild, 5·5% moderate, 1·3% severe) were matched to 1 809 029 patients without AD. Median age in the non-AD group was 4 years [interquartile range (IQR) 2–9] and median age across the three AD groups together was 4 years (IQR 1–8) to 9 years (IQR 4–14). There was a slight male predominance in all groups. Socioeconomic status was similar across the groups. Average follow-up duration was 5 years in the non-AD group and 5–7 years across the AD groups. Allergic rhinitis and asthma were more common among patients with AD (Table 1).

Incidence rates of infections are shown in Table S1 (see Supporting Information). Although herpesvirus infection occurred with an incidence of 21·1 per 1000 person-years (PY) among those without AD and 22·9–33·6 per 1000 PY among those with AD, the majority were caused by VZV and HSV. Serious infections occurred more frequently in patients with AD, ranging from 6·3 per 1000 PY in the mild and moderate groups to 8·1 per 1000 PY in the severe group, in contrast to 4·3 per 1000 PY in the non-AD group. Opportunistic infections were rare, with an incidence of 8–11 per 100 000 PY across the groups.

In adjusted Cox regression analysis, AD was associated with greater risk of any herpesvirus infection [hazard ratio (HR) 1·37, 95% confidence interval (CI) 1·36–1·38]) compared with non-AD, and risk increased with worsening severity of AD (mild: HR 1·34, 95% CI 1·33–1·36; moderate: HR 1·65, CI 1·60–1·70; severe: HR 1·81, 95% CI 1·72–1·91). Children with AD were at greater risk for CMV (HR 2·50, 95% CI 1·38–4·54), HSV (HR 1·52, 95% CI 1·48–1·56) and VZV (HR 1·33, 95% CI 1·32–1·35), with risk increasing in a ‘dose-dependent’ manner with worsening AD severity. While EBV risk was slightly elevated among patients with mild AD (HR 1·09, 95% CI 1·04–1·16) compared with patients without AD, risk was lower among patients with moderate (HR 0·88, 95% CI 0·78–0·99) and severe AD (HR 0·57, 95% CI 0·42–0·78). Patients with AD had a 40% higher risk of hospitalized infection compared with patients without AD (HR 1·40, 95% CI 1·38–1·43); stratified by AD severity, this risk was even higher among those with moderate AD (an 86% increase) and severe AD (a 2-fold increase) (Table 2). Finally, opportunistic infection risk was not statistically significantly different between the AD and non-AD groups. Adjusted risk differences are shown in Table S2 (see Supporting Information).

Adult cohort

A total of 625 083 patients with AD (65·7% mild, 31·4% moderate, 2·9% severe) were matched to 2 678 888 patients without AD. Median age was 45–50 years across the AD groups and 47 years in the non-AD group. All groups showed a female predominance. BMI, smoking and drinking status and socioeconomic status were generally similar between the AD and non-AD groups. Duration of follow-up was about 5 years, with slightly longer follow-up among those with moderate or severe AD. Baseline comorbidities are in Table 3.

The incidence of herpesvirus infections was 9·3, 9·9 and 12·5 per 1000 PY among adults with mild, moderate or severe AD, respectively, in contrast to 7·3 per 1000 PY among those without AD; HSV and VZV comprised most of these infections while CMV and EBV were much less common (Table S1). Serious infections occurred with an incidence of 6·9 per 1000 PY among patients without AD, while rates were higher and ranged from 8·0 to 13·5 per 1000 PY in those with AD. Opportunistic infections were rare but incidence was higher among patients with AD and increased with worsening AD severity (Table S1).

Comparing adults with AD to those without AD, the former were at greater adjusted risk for herpesvirus infection (HR 1·26, 95% CI 1·25–1·28), with the highest risk among those with severe AD (1·60, 95% CI 1·53–1·68) (Table 2). Patients with AD demonstrated higher risk for HSV (HR 1·50, 95% CI 1·46–1·53) and VZV (1·18, 95% CI 1·16–1·19) across all severity levels, with greatest risk in the severe AD group. AD was also associated with greater risk of EBV (HR 1·13, 95% CI 1·03–1·24) but this was mostly driven by severe AD (1·54, 95% CI 1·09–2·19). While mild and moderate AD were not significantly associated with CMV, those with severe AD had a 4·5-fold increase in risk of CMV infection compared with those without AD. Serious infections were also significantly associated with AD, with HRs ranging from 1·17 (95% CI 1·15–1·19) in mild AD to 1·68 (95% CI 1·61–1·76) in severe AD. Opportunistic infection risk was significantly elevated in patients with AD across all severities (mild: HR 1·12, 95% CI 1·001–1·26; moderate: 1·41, 95% CI 1·25–1·59; severe: 2·54, 95% CI 2·01–3·23) compared with patients without AD. Adjusted risk differences are shown in Table S2.

Sensitivity analyses restricted to patients with annual GP follow-up, ≥ 5 years' follow-up, or ≥ 1 year of observation time prior to cohort entry did not differ from the primary findings (Table S3; see Supporting Information). Analyses using maximum rather than time-updated AD severity or excluding patients with asthma or allergic rhinitis also resulted in similar findings. For EBV in children, using maximum AD severity led to HRs of 1·08 (95% CI 1·02–1·14), 1·10 (95% CI 0·99–1·22) and 0·85 (95% CI 0·67–1·09) for mild, moderate and severe AD, respectively. When HSV infections were excluded from the composite herpesvirus outcome and skin/soft tissue infections were excluded from the serious infection outcome, associations between AD and these outcomes remained unchanged, with only slight attenuation of effect sizes in the severe AD group. In analyses excluding patients receiving azathioprine, ciclosporin, methotrexate or mycophenolate, results remained similar; compared with patients without AD, both children and adults continued to have greater risk for herpesvirus infection [overall HRs 1·37 (95% CI 1·36–1·38) and 1·27 (95% CI 1·25–1·29), respectively] and serious infection [1·40 (95% CI 1·38–1·43) and 1·26 (95% CI 1·25–1·28), respectively], and adults still had greater risk for opportunistic infections (1·33, 95% CI 1·22–1·45).

Discussion

In this study, AD was associated with increased risk of several herpesvirus infections, hospitalized infections and opportunistic infections, with more severe AD portending greater risk. These associations were independent of other atopic illnesses and persisted in the

absence of immunosuppressive medication, suggesting that AD itself confers susceptibility to infections.

Susceptibility to cutaneous infections in AD has been attributed to epidermal barrier defects and decreased antimicrobial peptide expression in the skin.[2,23] Systemic immune dysregulation has also been demonstrated in patients with AD, with perturbations noted in both the adaptive and innate immune systems.[1,24–26] In genome-wide association studies of AD, polymorphisms have been identified in genetic loci that regulate T-cell function, innate host defences and skin barrier function.[27] Thus, increased infection risk in AD likely results from multiple factors including skin barrier defects, systemic immune dysregulation and immunosuppressive effects of therapy.

HSV infections are recognized complications of AD but few epidemiological studies have directly examined their association.[4,6,11] We found an overall 50% greater risk of HSV among children and adults with AD compared with those without AD, with an absolute risk increase of 1·9–3·5 per 1000 PY in severe AD compared with controls. Previous cross-sectional studies have also suggested that EH is rare among patients with AD but tends to be more common in those with severe AD.[4,6] The findings of our cohort study support these hypotheses; we observed incidence rates of 1·5–95 per 100 000 person-years for EH among patients with AD, with higher rates among children and patients with more severe AD.

Epidemiological data surrounding other herpesvirus infections in AD are also sparse. In cross-sectional US surveys, varicella and herpes zoster were more commonly reported by patients with AD presenting to emergency departments.[7,8,28] Building on this earlier work, our cohort study shows that AD is associated with greater incidence of VZV infection and reactivation, and that worsening AD severity is associated with increasing infection risk. Previous studies of EBV and CMV infections in AD have demonstrated inconsistent findings. Although some have reported higher EBV antibody titres and greater prevalence of subclinical CMV infection in patients with AD, others have not found an association between CMV or EBV seropositivity and AD.[12–15,29,30] Our findings suggest that AD is associated with greater incidence of CMV infection among both children and adults, particularly those with severe AD. EBV infection risk was primarily elevated among adults with severe AD. Interestingly, among children, mild AD was associated with a slightly increased risk of EBV infection, while moderate-to-severe AD appeared protective against EBV. Sensitivity analyses using maximum rather than time-updated AD severity were conducted to explore the possibility of a ‘depletion of susceptibles’ phenomenon. These analyses showed an association between EBV and mild AD but no significant association with moderate or severe AD, suggesting that some of the observed inverse associations with moderate-to-severe AD in the primary analysis may be partly due to the time-updated nature of severity definitions.

Our study also adds to the growing evidence that AD increases susceptibility to extracutaneous infections. US cross-sectional surveys have demonstrated greater prevalence of influenza/pneumonia, streptococcal throat infection (strep throat), sinus infection, gastroenteritis, ear infections and urinary tract infections in both children and adults with

AD.[7,8] One case–control study of a community sample found a 2·5-fold greater odds of pneumococcal infection among adults with AD.[31] In a previous study using THIN, higher odds of otitis media, pneumonia and strep throat were observed in patients with AD compared with non-AD control participants at any time before or after AD diagnosis.[9] Our study adds to the literature by examining multiple additional types of infections and focusing on incident infections after AD diagnosis. To date, the association between AD and serious infections has only been examined in a cross-sectional manner using a sample of US hospitalization data, where AD was associated with greater odds of skin and respiratory infections, endocarditis, encephalitis and bone/joint infections.[32,33] By employing a cohort design, our study found that the incident risk of serious infection was 34–200% higher among children and 17–68% higher among adults with AD compared with patients without AD, with the greatest risk manifesting among those with severe AD. To our knowledge, this study is also one of the first to evaluate the risk of opportunistic infections in patients with AD. Although children were not at statistically significantly greater risk of opportunistic infections, adults with moderate or severe AD had a risk up to 2·5-fold greater. These estimates remained similar in sensitivity analyses excluding patients who received immunosuppressive medications. Taken together, this suggests that adults with moderate-to-severe AD may have significant immune dysfunction.

Our study has several strengths. Firstly, while most studies have been cross-sectional, our cohort study design enabled an assessment of the temporal relationship between AD and infectious outcomes as well as estimation of incident risk. Secondly, our study is one of the first to evaluate the impact of AD severity on infectious comorbidities; the observation of increasingly greater infection risk in individuals with more severe AD supports the notion that the skin condition is a driver of susceptibility to infection. Thirdly, we used a large, generalizable medical records database validated for the study of AD,[16] in contrast to previous studies, which have primarily relied on patient self-report or less representative clinic-based populations.

There are potential limitations to note. As treatments served as proxies for AD severity, we cannot separate severity effects from treatment effects. However, exclusion of patients receiving systemic immunosuppressive medications did not alter our findings, suggesting that infection risk is not entirely driven by therapy-related immunosuppression. Potential misclassification of AD severity is also possible but this approach is commonly used in epidemiological investigations of AD, as direct measures of severity are not routinely captured in electronic medical records.[18,19] Additionally, although AD severity was treated as a time-updated variable to allow for escalation in disease severity over time, severity may also de-escalate, as AD waxes and wanes by nature. Thus, it is possible that some cases of AD defined as moderate or severe may subsequently become milder in severity; nevertheless, such potential misclassification would be expected to bias our results toward the null. Misclassification of outcomes is also possible, but we would expect it to be nondifferential, that is not to vary systematically by AD status. As THIN includes only GP-recorded data, hospitalization data may also be less comprehensive; however, details on hospital admissions are typically sent to GPs and recorded in THIN. Ascertainment bias is another potential limitation if patients with AD were more likely to see their GP than were

patients without AD; however, our sensitivity analyses restricted only to patients seen at least yearly yielded similar results.

In conclusion, AD is associated with increased risk of herpesvirus infections, hospitalized infections and opportunistic infections, independent of other atopic disorders and common risk factors for infection. Importantly, as novel immunomodulatory medications, including biologics and Janus kinase inhibitors, continue to emerge for the treatment of AD, an understanding of infection risk in AD will be critical for informing treatment selection for patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

J.W. has received research and fellowship funding from Pfizer, Inc. (*paid to the University of Pennsylvania*). *M.N.S. has received fellowship funding from Pfizer, Inc.* (*paid to the University of Pennsylvania*). *K.A. has received research funding from Pfizer, Inc. and L'Oréal* (*paid to UCSF*), *and receives consulting fees for serving on the academic steering committee for TARGET RWE. A.R.L. is an employee of Pfizer, Inc. J.M.G. has served as a consultant for and received honoraria from Abcentra, AbbVie, Bristol Myers Squibb, Boehringer Ingelheim, GSK, Eli Lilly and Company* (*data monitoring committee*), *Janssen Biotech, Novartis, UCB* (*data and safety monitoring board*), *Neuro-Derm* (*data and safety monitoring board*), *Trevi Therapeutics Inc., and MiNDERA Dx* (*Mindera Health*); *he receives research grants* (*to the trustees of the University of Pennsylvania*) *from Boehringer Ingelheim and Pfizer Inc.; he has received payment for continuing medical education work related to psoriasis that was supported indirectly by pharmaceutical sponsors; he is a co-patent holder of resiquimod for treatment of cutaneous T-cell lymphoma; he serves as a deputy editor for the* Journal of Investigative Dermatology, *receiving honoraria from the Society for Investigative Dermatology; he is Chief Medical Editor for* Healio Psoriatic Disease (*receiving honoraria*); *and he is a member of the board of directors for the International Psoriasis Council, receiving no honoraria. D.B.S. declares he has no conflicts of interest.*

Data availability statement

The data that support the findings of this study are available from IQVIA. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the authors, with the permission of IQVIA.

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What is already known about this topic?

- Atopic dermatitis (AD) is associated with infectious complications, most commonly staphylococcal and herpes simplex virus infections.
- However, the risk of serious infections, opportunistic infections and other herpesvirus infections in patients with AD has not been fully characterized.

What does this study add?

- AD is associated with an increased risk of hospitalized infections, opportunistic infections and several herpesvirus infections in both children and adults, with risk being greatest among those with severe skin disease.
- The elevated risks of these infections appear independent of immunosuppressive medication use for AD.

Table 1

Baseline characteristics of paediatric cohort, aged < 18 years, in The Health Improvement Network® (THIN®) database, 1994–2015

Characteristic	Control n = 1 809 029	Mild AD n = 381 678	Moderate AD n = 22 433	Severe AD n = 5320
Age, median (IQR), years Sex	4 (2–9)	4 (1–8)	9 (4–14)	5 (1–10)
Sex				
Female	872 279 (48·22)	184 682 (48·39)	11 054 (49·28)	2335 (43·89)
Male	936 750 (51·78)	196 996 (51·61)	11 379 (50·72)	2985 (56·11)
Townsend deprivation index				
1 Lowest	424 409 (24·71)	89 820 (24·89)	4768 (22·55)	1251 (25·00)
2 Low	340 677 (19·84)	71 979 (19·95)	4106 (19·42)	1069 (21·37)
3 Moderate	355 559 (20·70)	75 261 (20·86)	4551 (21·52)	1033 (20·65)
4 High	339 336 (19·76)	70 649 (19·58)	4316 (20·41)	900 (17·99)
5 Highest	257 540 (14·99)	53 113 (14·72)	3407 (16·11)	750 (14·99)
Unknown	91 508 (5·06)	20 856 (5·46)	1285 (5·73)	317 (5·96)
PY per 1000, median (IQR)	4·99 (2·0–9·4)	5·22 (2·1–9·7)	6·02 (2·6–10·2)	6·89 (2·7–12·6)
Allergic rhinitis	75 050 (4·15)	23 935 (6·27)	2870 (12·79)	521 (9·79)
Asthma	169 679 (9·38)	49 782 (13·04)	6094 (27·17)	1222 (22·97)
Congestive heart failure	768 (0·04)	134 (0·04)	2 (0·01)	5 (0·09)
Chronic kidney disease	825 (0·05)	140 (0·04)	8 (0·04)	19 (0·36)
COPD	188 (0·01)	47 (0·01)	3 (0·01)	3 (0·06)
Depression	4318 (0·24)	797 (0·21)	158 (0·70)	15 (0·28)
Diabetes mellitus	2708 (0·15)	395 (0·10)	31 (0·14)	8 (0·15)
Inflammatory bowel disease	411 (0·02)	65 (0·02)	10 (0·04)	79 (1·48)
Liver disease	904 (0·05)	165 (0·04)	10 (0·04)	21 (0·39)
Prior influenza vaccination	33 292 (1·84)	6484 (1·70)	604 (2·69)	121 (2·27)
Prior meningococcal vaccination	35 889 (1·98)	8134 (2·13)	567 (2·53)	117 (2·20)
Prior pneumococcal vaccination	15 519 (0·86)	3343 (0·88)	112 (0·50)	28 (0·53)
History of herpesvirus infection[a]	288 140 (15·93)	64 421 (16·88)	4484 (19·99)	1062 (19·96)
History of opportunistic infection[b]	1045 (0·06)	237 (0·06)	29 (0·13)	4 (0·08)
History of serious infection[c]	69 218 (3·83)	15 919 (4·17)	716 (3·19)	221 (4·15)

All values are n (%) unless stated otherwise. AD, atopic dermatitis; PY, person-years; IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

[a]Herpesvirus infection includes cytomegalovirus, Epstein–Barr virus, herpes simplex virus and varicella zoster virus infections.

[b]Opportunistic infection includes actinomycosis/nocardiosis, aspergillosis, BK virus, cryptococcosis, cytomegalovirus, mucormycosis, other mycoses (blastomycosis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis), pneumocystis, progressive multifocal leukoencephalopathy, tuberculosis and toxoplasmosis.

[c]Serious infection includes infections of respiratory tract, urinary tract, gastrointestinal tract/abdominal cavity, bone or joints, central nervous system or meninges, heart, skin or soft tissue, prostate, breast, and eyes and sepsis requiring hospitalization.

Table 2

Adjusted hazard rate ratios (95% confidence intervals) [reference non-atopic dermatitis (AD) group] of infectious outcomes among children and adults with AD in The Health Improvement Network® (THIN®) database, 1994–2015

	Paediatric cohort[a] (aged < 18 years)				Adult cohort[b] (aged ≥ 18 years)			
Infectious outcome	**Overall AD**	**Mild AD**	**Moderate AD**	**Severe AD**	**Overall AD**	**Mild AD**	**Moderate AD**	**Severe AD**
Herpesvirus	**1·37** (1·36–1·38)	**1·34** (1·33–1·36)	**1·65** (1·60–1·70)	**1·81** (1·72–1·91)	**1·26** (1·25–1·28)	**1·22** (1·20–1·25)	**1·28** (1·26–1·31)	**1·60** (1·53–1·68)
CMV	**2·50** (1·38–4·54)	**2·33** (1·22–4·43)	2·30 (0·54–9·84)	**7·62** (1·66–35·0)	1·41 (0·92–2·17)	1·00 (0·54–1·84)	1·63 (0·88–3·01)	**4·45** (1·76–11·25)
EBV	1·04 (0·98–1·09)	**1·09** (1·04–1·16)	**0·88** (0·78–0·99)	0·57 (0·42–0·78)	**1·13** (1·03–1·24)	1·09 (0·98–1·22)	1·15 (0·98–1·33)	**1·54** (1·09–2·19)
HSV	**1·52** (1·48–1·56)	**1·44** (1·40–1·48)	**1·83** (1·72–1·94)	**2·66** (2·40–2·95)	**1·50** (1·46–1·53)	**1·41** (1·38–1·46)	**1·57** (1·52–1·63)	**1·95** (1·80–2·11)
EH	**32·7** (24·3–43·9)	**20·7** (15·3–28·2)	**125·7** (89·3–176·9)	**252·9** (174·3–366·9)	**19·9** (12·9–30·5)	**7·42** (4·31–12·78)	**28·3** (17·8–45·0)	**115·6** (68·4,195·4)
Non-EH	**1·46** (1·42–1·50)	**1·40** (1·36–1·44)	**1·68** (1·58–1·79)	**2·29** (2·04–2·56)	**1·49** (1·45–1·52)	**1·41** (1·37–1·45)	**1·56** (1·51–1·62)	**1·89** (1·75–2·05)
VZV	**1·33** (1·32–1·35)	**1·31** (1·30–1·32)	**1·59** (1·53–1·64)	**1·70** (1·60–1·80)	**1·18** (1·16–1·19)	**1·14** (1·12–1·16)	**1·18** (1·15–1·21)	**1·52** (1·44–1·61)
Herpes zoster	**1·10** (1·07–1·13)	**1·07** (1·04–1·11)	**1·17** (1·09–1·27)	**1·57** (1·38–1·79)	**1·17** (1·15–1·19)	**1·13** (1·11–1·16)	**1·18** (1·16–1·21)	**1·53** (1·44–1·62)
Opportunistic infection[c]	1·09 (0·94–1·28)	1·06 (0·90–1·25)	1·27 (0·86–1·88)	1·36 (0·64–2·86)	**1·31** (1·20–1·42)	**1·12** (1·001–1·26)	**1·41** (1·25–1·59)	**2·54** (2·01–3·23)
Serious infection[d]	**1·40** (1·38–1·43)	**1·34** (1·32–1·37)	**1·86** (1·77–1·95)	**2·01** (1·84–2·19)	**1·26** (1·24–1·27)	**1·17** (1·15–1·19)	**1·31** (1·28–1·33)	**1·68** (1·61–1·76)

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; EH, eczema herpeticum; VZV, varicella zoster virus. Tests for trend with P < 0·001 for all outcomes except EBV in the paediatric cohort (P = 0·42) and opportunistic infection in the paediatric cohort (P = 0·16).

[a]Adjusted for age, sex, Townsend score, allergic rhinitis, asthma, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, inflammatory bowel disease, liver disease, and vaccinations for influenza, meningococcus and pneumococcus.

[b]Adjusted for same covariates as paediatric cohort as well as body mass index, smoking and alcohol status.

[c]Opportunistic infection includes actinomycosis/nocardiosis, aspergillosis, BK virus, cryptococcosis, cytomegalovirus, mucormycosis, other mycoses (blastomycosis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis), pneumocystis, progressive multifocal leukoencephalopathy, tuberculosis and toxoplasmosis.

[d]Serious infection includes infections of respiratory tract, urinary tract, gastrointestinal tract/abdominal cavity, bone or joints, central nervous system or meninges, heart, skin or soft tissue, prostate, breast, and eyes and sepsis requiring hospitalization. Statistically significant hazard rate ratios with P < 0·05 are in bold.

Table 3

Baseline characteristics of adult cohort, aged ≥ 18 years, in The Health Improvement Network® (THIN®) database, 1994–2015

Characteristic	Control n = 2 678 888	Mild AD n = 410 867	Moderate AD n = 196 101	Severe AD n = 18 115
Age, median (IQR), years	47 (32–64)	45 (30–63)	50 (34–68)	47 (32–63)
Sex				
Female	1 445 589 (53·96)	256 071 (62·32)	109 404 (55·79)	10 736 (59·27)
Male	1 233 299 (46·04)	154 796 (37·68)	86 697 (44·21)	7379 (40·73)
Body mass index, kg m^{-2}				
Underweight (< 18)	72 655 (2·71)	11 504 (2·80)	4150 (2·12)	525 (2·90)
Normal (18·5–24·9)	911 449 (34·02)	152 480 (37·11)	66 015 (33·66)	6972 (38·49)
Overweight (25–29·9)	707 292 (26·40)	109 693 (26·70)	56 021 (28·57)	4799 (26·49)
Obese (30–34·9)	285 567 (10·66)	44 998 (10·95)	24 088 (12·28)	1900 (10·49)
Severely obese (35–39·9)	94 373 (3·52)	15 720 (3·83)	8486 (4·33)	653 (3·60)
Morbidly obese (> 40)	44 721 (1·67)	8341 (2·03)	4525 (2·31)	343 (1·89)
Unknown	562 831 (21·01)	68 131 (16·58)	32 816 (16·73)	2923 (16·14)
Smoking status				
Never	1 293 811 (48·30)	206 577 (50·28)	89 588 (45·68)	8653 (47·77)
Current	576 463 (21·52)	84 855 (20·65)	44 195 (22·54)	3914 (21·61)
Former	548 828 (20·49)	92 290 (22·46)	48 636 (24·80)	4182 (23·09)
Unknown	259 786 (9·70)	27 145 (6·61)	13 682 (6·98)	1366 (7·54)
Drinking status				
Never	300 614 (11·22)	51 208 (12·46)	24 278 (12·38)	2338 (12·91)
Current	1 655 958 (61·82)	262 008 (63·77)	125 921 (64·21)	11 525 (63·62)
Former	114 596 (4·28)	19 708 (4·80)	10 187 (5·19)	965 (5·33)
Unknown	607 720 (22·69)	77 943 (18·97)	35 715 (18·21)	3287 (18·15)
Townsend deprivation index				
1 Lowest	677 724 (26·39)	102 924 (26·20)	46 708 (24·99)	4685 (27·26)
2 Low	564 890 (22·00)	84 924 (21·61)	40 579 (21·71)	3821 (22·23)
3 Moderate	534 554 (20·82)	81 331 (20·70)	39255 (21·00)	3566 (20·75)
4 High	468 773 (18·25)	73 004 (18·58)	35 452 (18·97)	3038 (17·67)
5 Highest	322 027 (12·54)	50 711 (12·91)	24 936 (13·34)	2079 (12·09)

Characteristic	Control n = 2 678 888	Mild AD n = 410 867	Moderate AD n = 196 101	Severe AD n = 18 115
Unknown	110 920 (4·14)	17 973 (4·37)	9171 (4·68)	926 (5·11)
PY per 1000, median (IQR)	4·96 (2·09–9·18)	4·94 (2·05–9·24)	5·20 (2·204–9·44)	5·41 (2·14–10·44)
Allergic rhinitis	266 083 (9·93)	66 023 (16·07)	29 926 (15·26)	3062 (16·90)
Asthma	346 024 (12·92)	80 267 (19·54)	42 608 (21·73)	4584 (25·30)
Congestive heart failure	45 960 (1·72)	7529 (1·83)	4874 (2·49)	369 (2·04)
Chronic kidney disease	73 550 (2·75)	10 835 (2·64)	6903 (3·52)	945 (5·22)
COPD	62 537 (2·33)	10 253 (2·50)	7064 (3·60)	591 (3·26)
Depression	526 849 (19·67)	97 510 (23·73)	46 401 (23·66)	4164 (22·99)
Diabetes mellitus	139 798 (5·22)	21 014 (5·11)	12 276 (6·26)	931 (5·14)
Inflammatory bowel disease	21 204 (0·79)	3397 (0·83)	1852 (0·94)	1730 (9·55)
Liver disease	28 890 (1·80)	4800 (1·17)	2566 (1·31)	409 (2·26)
Prior influenza vaccination	411 603 (15·36)	69 247 (16·85)	39 315 (20·05)	4026 (22·22)
Prior meningococcal vaccination	29 938 (1·12)	5765 (1·40)	2468 (1·26)	277 (1·53)
Prior pneumococcal vaccination	139 513 (5·21)	21 737 (5·29)	12 964 (6·61)	1262 (6·97)
History of herpesvirus infection[a]	315 288 (11·77)	62 857 (15·30)	26 864 (13·70)	3043 (16·80)
History of opportunistic infection[b]	24 061 (0·90)	4099 (1·00)	2192 (1·12)	248 (1·37)
History of serious infection[c]	67 432 (2·52)	13 167 (3·20)	6878 (3·51)	944 (5·21)

All values are n (%) unless otherwise stated. AD, atopic dermatitis; IQR, interquartile range; PY, person-years; COPD, chronic obstructive pulmonary disease.

[a]Herpesvirus infection includes cytomegalovirus, Epstein–Barr virus, herpes simplex virus, and varicella zoster virus infections.

[b]Opportunistic infection includes actinomycosis/nocardiosis, aspergillosis, BK virus, cryptococcosis, cytomegalovirus, mucormycosis, other mycoses (blastomycosis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis), pneumocystis, progressive multifocal leukoencephalopathy, tuberculosis and toxoplasmosis.

[c]Serious infection includes infections of respiratory tract, urinary tract, gastrointestinal tract/abdominal cavity, bone or joints, central nervous system or meninges, heart, skin or soft tissue, prostate, breast, and eyes and sepsis requiring hospitalization.