Risk of systemic infections in adults with atopic dermatitis: a nationwide cohort study

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Capsule summary

- Adult AD patients managed in a hospital setting have a significantly higher risk of having systemic infections but the absolute risk increase was generally small.
- Clinicians should be aware of the increased risk of musculoskeletal, heart and respiratory tract infections when managing adults with AD.

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Abstract

Background: Atopic dermatitis (AD) has been linked to systemic infections in adulthood, but large-scale studies are few and potential associations unclear.

Objective: To examine whether adults with AD have increased risk of developing systemic infections leading to hospital-based management.

Methods: Nationwide register-based cohort study including all Danish adults from 1995 through 2017. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox models.

Results: 10,602 adults with AD (median age 29.8 years, interquartile range 22.6-44.8) and 106,020 reference individuals were included. The overall incidence rate per 10,000 person-years of systemic infections was 180.6 (95%CI 172.6-189.0) among AD adults compared with 120.4 (95%CI 118.3-122.5) among reference adults. The association between AD and systemic infections was observed for musculoskeletal (adjusted HR [aHR] 1.81, 95%CI 1.42-2.31), heart (aHR 1.75 95%CI 1.21-2.53), upper (aHR 1.42 95%CI 1.15-1.73) and lower respiratory tract infections (aHR 1.21 95%CI 1.10-1.33). The risk of sepsis (aHR 1.19 95%CI 1.01-1.44) and skin infections (aHR 2.30 95%CI 2.01-2.62) was also increased.

Limitations: The findings cannot be generalized to adults with milder AD seen outside the hospital system.

Conclusion: We found an increased risk of systemic infections among adults with hospital managed AD.

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Capsule summary

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- Clinicians should be aware of the increased risk of musculoskeletal, heart and respiratory tract infections when managing adults with AD.

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INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease in adults.[1] Patients with AD have increased risk of bacterial and viral skin infections,[2-8] in part due to alterations in the molecular composition of the skin barrier and an altered cell mediated immune response.[9-11] The use of systemic immunosuppressants may further reduce host immune response.

It is currently unclear whether AD patients also have an increased risk of developing systemic infections. In theory, untreated *Staphylococcus aureus* (*S.aureus*) skin infections in patients with AD may lead to invasion and development of e.g. endocarditis and sepsis, as previously reported in patients with AD.[12-17] A recent systemic review including seven studies concluded that AD patients had higher odds of ear, strep throat and urinary tract infections,[17] but also clearly emphasized the scarcity of data.

This nationwide registry-based study examined whether adults with AD had increased risk of systemic infections compared to adults from the general population.

MATERIAL AND METHODS

Data sources

We used the Danish national medico-administrative registries, covering the entire population. They contain anonymous, individual data, including demographic data;[18,19] inpatient, outpatient, and emergency room visit diagnostic data and all hospital procedures from all public hospitals and a number of private hospitals in the Danish National Patient Register (DNPR)[20-23]; all drug dispensations from pharmacies (according to the Anatomical Therapeutic Chemical classification, ATC) with their date of dispensations in the Danish National Prescription Register (DNPrR)[24]; the household and personal income data in the

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Income Statistic Register.[25] All registers are linked thanks to a unique ten-digit personal identifier given to each Danish resident.[18]

Inclusion criteria

All adults (≥18 years) between January 1, 1995 and December 31, 2017, were included in the source population. Exposed individuals (AD adults) were adults with a hospital International Classification of Diseases 10th revision (ICD-10) primary diagnosis (inpatient or outpatient) of AD (L20.x) given by a hospital-based dermatologist in adulthood at any time during the study period. The positive predictive value of AD diagnosis in the Danish registries is 92% in adults.[26] Each AD adult was randomly matched with 10 unexposed individuals (reference adults), without an in- or outpatient hospital diagnosis of AD in adulthood or childhood, on birth date and gender at the date of first AD diagnosis, identified through the DNPR (general population).

Outcomes

Study outcomes were systemic infections leading to hospital management (hospitalizations, visits to emergency departments, or outpatient hospital visits), identified through the hospital discharge ICD-10 codes (Supplemental Table 1).[27] Only primary diagnoses were analyzed. Systemic infections were categorized based on the specific organ that was affected and not the specific pathogen. However, we studied separately two AD associated pathogens and defined these categories as '*Staphylococcal* infections' (*S.aureus*, skin and systemic) and 'Herpes infections' (herpes simplex, skin and systemic).

Follow-up

In a cohort study, we examined the risk of developing a study outcome (an in- or outpatient hospital diagnosis of infections) beginning from the date of first AD diagnosis (index date). Reference individuals were followed from the date of AD diagnosis for the corresponding AD individuals. Follow-up ended at the time of first recorded infection, study end date (December

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31, 2017), migration or date of death, whichever occurred first. All individuals contributing with at least one day of follow-up were included.

Covariates

A directed acyclic graph was performed to represent the covariates and intermediate factors to avoid collider bias.[28] Asthma and hay fever were defined by at least one ICD-10 hospital diagnosis (J45-J46, J30) [29] recorded in the DNPR (given between two years before the index date and study end). Smoking and alcohol abuse were assessed using algorithms as described previously (yes/no, ever in the follow-up period). [30,31] The socioeconomic level was assessed by the average household income within the five years before the index date. Medical chronic comorbidities were assessed using the Charlson comorbidity index (CCI) (at least within seven years before the index date) (Supplemental Table 2).[32] Systemic immunosuppressant use for AD (Supplemental Text 1) was assessed after the index date. Systemic corticosteroid use was defined by a least one dispensation within three months before the index date or in study period (Supplemental Text 1).

The level of AD activity was assessed over time. Active AD was defined by at least two eczema hospital entries (on separated dates) a year in their records for more than half of their follow-up period, with a least five years of follow-up.[33] An entry means either visit for AD or dispensation of treatment for AD (Supplemental Text 1).

The severity of AD was defined according to the dispensations of all treatments used in Denmark for AD (topical and systemic immunosuppressant) and included four categories: severe, moderate-to-severe, mild-to-moderate and mild (see Supplemental Text 1).

Statistical analysis

Cohorts characteristics were summarized descriptively. Incidence rates (IRs) were estimated by identifying the number of incident infections and the number of person-years of follow-up. Person year time for each patient was calculated as the time from the index date to the end of

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follow-up, for each infection. To estimate the population impact of AD on infection risk, we calculated the absolute risk difference with 95% confidence intervals (95%CI) for each infection as the difference between unexposed and exposed cohort's IRs. The attributable fraction of each infection among the AD population was estimated (proportion of infections attributable to AD among AD population).

We used Cox proportional hazards regression models with calendar time as the underlying timescale to estimate hazard ratios (HRs) with 95%CI of the association between AD and each category of infection and with the general population as the reference group (crude model). Adjustments were performed for covariates, which may have been on the causal pathway between AD and infections, i.e. atopic comorbidities (asthma and/or hay fever, time-updated variables), smoking and alcohol abuse (yes/no), general comorbidities (CCI at cohort entry), socioeconomic status (at cohort entry) and AD immunosuppressant treatments (time-updated variable). We used the log graphic method to test hazard proportional assumptions. Stratified analyses were conducted according to gender, age group (18 to 39 years and over 39 years), use of systemic corticosteroid (yes/no) and AD severity.

Sensitivity analyses

We performed a sensitivity analysis by only including infections leading to hospitalization (>24 hours). We also performed a sensitivity analysis to examine the association between AD and possible hospital-acquired infections by investigating only secondary diagnosis of infections in hospitalized patients under the assumption that many infections coded as secondary diagnosis were hospital-acquired.

Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, U.S.A.) and Stata v15.0 (StataCorp, College Station, USA).

This study followed the STROBE guidelines for reporting.[36]

Access authorizations

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Approval from an ethics committee is not required for register studies in Denmark.

RESULTS

Cohorts characteristics

In total, 10,602 adults with AD and 106,020 reference matched adults were included in the cohort (Figure 1). The median age was 29.8 (interquartile range [IQR], 22.6-44.8) years, and 63.0% were women (Table 1). Among AD patients, 20.8% had received at least one systemic immunosuppressant for AD at any time, and 94.5% had presumed active AD. The prevalence of hospital-diagnosed atopic comorbidities was higher in the AD population than in the general population during follow-up (25.1% vs 3.1%, p<0.0001).

A total of 22,809 systemic infections were identified: 3,127 infections (mean 0.6+/-1.9 per individual) in the AD population during a follow-up of 103,787 years (median 3,575; IQR 1,280-5,772), compared to 19,682 infections (mean of 0.3+/-0.9 per individual) in the general population during a follow-up of 1,078,576 years (median 3,716; IQR 1,386-5,946). We observed increased IRs of all systemic infections among the AD population (Table 2). For example, the IRs per 10,000 person-years of lower respiratory tract and heart infections were 58.03 (95%CI 53.74-62.67) and 3.65 (95%CI 2.70-4.94) among AD adults compared with 33.67 (95%CI 32.62-34.75) and 1.85 (95%CI 1.61-2.12) among reference adults, respectively. The highest population attributable risks among the AD population were for musculoskeletal infections (53.0%, 95%CI 42.0-62.0) and heart infections (49.0%, 95%CI 27.0-63.0).

Time to first infection associated with AD during adulthood

The crude and multivariable-adjusted HRs for the association between AD and systemic infections are presented in Table 3 and Figure 2. The strongest associations were for musculoskeletal infections (adjusted HR [aHR] 1.81 95%CI 1.42-2.31), heart infections (aHR 1.75 95%CI 1.21-2.53), upper and lower respiratory tract infections (aHR 1.42 95%CI 1.15-1.73 and aHR 1.21 95%CI 1.10-1.33), sepsis (aHR 1.19 95%CI 1.01-1.44) and skin infections

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(aHR 2.30 95%CI 2.01-2.62). No association was observed for gastrointestinal tract, urinary tract, and nervous system infections. AD was also associated with herpes (aHR 5.28 95%CI 3.47-8.02) and staphylococcal infections (aHR 2.11 95%CI 1.75-2.56) in adulthood.

The analyses stratified by gender, age groups, systemic corticosteroid use and AD severity are given in Supplemental Table 3, Table 4, Figures 1, 2 and 3. The results were quite similar for men and women with AD, except for herpes with higher risk observed among men (aHR 14.00 95%CI 6.62-29.63 vs. 3.47 95%CI 2.05-5.88). We observed slightly higher HR for upper respiratory tract infections (aHR 1.46 95%CI 1.18-1.82), sepsis (aHR 1.61 95%CI 1.16-2.25) and herpes infections (aHR 5.52 95%CI 3.49-8.74) in younger AD patients compared to older AD patients (aHR 1.16 95%CI 0.66-2.02; 1.05 95%CI 0.83-1.33; 4.59 95%CI 1.65-12.78; respectively). The association increased with the AD severity for lower respiratory tract infections, musculoskeletal tract infections, heart infections and sepsis.

Sensitivity analyses

In the analyses restricted to infections which lead to hospitalization (>24 hours), AD was associated with lower respiratory tract infections (aHR 1.19 95%CI 1.06-1.32) and heart infections (aHR 1.64 95%CI 1.09-2.48), but not with musculoskeletal infections (aHR 1.39 95%CI 0.97-1.99), upper tract infections (aHR 1.35 95%CI 0.94-1.93) and sepsis (aHR 1.19 95%CI 0.99-1.44) (Supplemental Tables 5, 6 and Figure 4).

In the analyses restricted to only secondary diagnoses of infections, the HRs were similar or higher relative to those including only primary diagnosis of infections, for lower respiratory tract infections (aHR 1.26 95%CI 1.06-1.49), musculoskeletal infections (aHR 2.29 95%CI 1.16-4.53) and sepsis (aHR 1.55 95%CI 1.14-2.12). No association was observed for upper respiratory tract (aHR 0.37 95%CI 0.04-3.12) and heart infections (aHR 1.44 95%CI 0.62-3.34) (Supplemental Tables 7, 8 and Figure 5).

DISCUSSION

Main findings

This nationwide registry-based study showed that adults with a hospital diagnosis of AD had an increased risk of developing systemic infections affecting the heart, the musculoskeletal system, and the respiratory tract as well as sepsis and skin infections compared with non-AD adults. The population attributable risks were high for heart and musculoskeletal system infections.

Interpretation

Several pathophysiological mechanisms could explain the possible association between AD and the increased susceptibility to systemic and skin infections. These include elevated skin pH allowing staphylococci to colonize the skin, insufficient up-regulation and synthesis of antimicrobial peptides and filaggrin known to reduce staphylococci growth,[35,36] and reduced skin microbiota diversity with increased colonization by *S.aureus*.[37] The association between AD and susceptibility loci related to immune regulation, in particular innate host defenses and T-cell function, may also be important.[10,11] Because AD patients with very active lesions have high density of *S.aureus,* they could be at particular risk of sepsis and endocarditis. This may be explained by superinfection of active lesions that become invasive, or via intravascular interventions.[38,39]

Our results provide strong evidence of an association between AD and potentially life-threatening infections including endocarditis and sepsis. These findings support the clinical relevance of case reports of infective endocarditis concomitant with eczema flares.[12,14,15] Two cross-sectional studies, using the 2002-2012 National Inpatient Sample in the United States, also found higher prevalence of endocarditis and septicemia.[40,41] A recent study based on the Danish registries showed the death due to cardiovascular and infectious diseases were increased in AD adults compared with adults without AD.[42] The observed increased risk for heart infections might explain a part of these specific deaths. Furthermore, the population

attributable fraction of 49% for heart infections among the AD adults' population is high and might be due to the high density of *S.aureus* in lesional skin.[38] Interestingly, *S.aureus* bloodstream infections in AD patients seem to be hospital-acquired in about 60% of cases with skin infections and intravascular catheters as the main portals of entri.[39] We also found higher risk of presumed hospital-acquired sepsis and 'staphylococcal infections' among AD adults, by investigating separately primary and secondary diagnoses of infections given in the hospital system.

The observed increased risk for heart infections and sepsis should be however interpreted with caution. Indeed, the absolute risk difference for heart infections is small, corresponding to 1.8 additional heart infections among AD adults over a 20-year period.

The increased risk for musculoskeletal infections has not been reported before from a population-based study. Nonetheless, few cases of osteomyelitis or arthritis due to *S.aureus* in context of AD has been reported and the authors postulated that skin was the source of the infections through a trauma.[43-45] Our design could not however address this hypothesis. A review and meta-analysis concluded that patients with AD have higher prevalence of infections affecting the ears, throat and urinary tract.[17] One additional study using a UK general practitioner medical records database showed as well increased risks of otitis media, pneumonia and streptococcal throat infections in AD patients but only focused on the respiratory tract and did not study infections with hospital management.[46] We did not confirm the association with urinary tract infections and reported in addition an increased risk for musculoskeletal infections. The studies included in this meta-analysis had important limitations. Six of seven studies had a cross-sectional design,[40,41,47-50] diagnoses were self-reported in 4 studies,[47-50] and only 2 studies examined adult patients.[41,50] Lastly, the number of musculoskeletal infections observed in each group is relatively high and could not be a random effect.

Strengths and limitations

Study strengths include the exhaustive nationwide coverage of the Danish population with all dermatologist-diagnosed AD patients who were seen in a hospital setting with no attrition bias, no loss of follow-up over 20 years, and the consideration of different category of systemic infections. While we attempted to take potential confounders into consideration, we cannot exclude residual confounding. It was a study weakness that our patient cohort was entirely hospital-based with more severe spectrum of AD and we therefore cannot determine the clinical relevance of our findings for milder AD cases. We only assessed adults from dermatology departments assuming that AD patients with hospital health contact care have probably active disease and therefore are at risk of infections. We know that AD adults referred to hospital have higher risk of comorbidities and smoking and alcohol abuse.[51,52] These confounding factors were however taken into account by matching on age, by adjustment using the CCI as well as hospital diagnoses of asthma and by adjustment for smoking and alcohol. Even if patients with chronic skin disease are more likely to have health care and clinical screening with skin infections diagnosed than the general population, we believe that there is no differential recording for systemic infections.

Finally, we did not have information about relative severity of infections nor the pathogens involved except the focus on staphylococcal and herpes simplex infections.

CONCLUSION

We found that adult patients with AD had a higher risk of being diagnosed with systemic infections including life-threatening ones such as endocarditis and sepsis. Clinicians should be aware of these potential associations when managing adults with AD.

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Abbreviations used

AD, Atopic dermatitis

aHR, adjusted HR

ATC, Anatomical Therapeutic Chemical classification

CI, Confidence Interval

DNPR, Danish National Patient Register

DNPrR, Danish National Prescription Register

HR, Hazard Ratio

ICD-10, International Classification of Diseases 10th revision

IQR, Interquartile Range

S.aureus, *Staphylococcus aureus*

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Tables

Table 1: Descriptive characteristics of the non-exposed cohort (general population) and the exposed cohort (atopic dermatitis population) at index date

	General population N=106,020	Adulthood AD* population N=10,602	Overall population N=116,622
Gender, n (%)			
Male	39,270 (37.0)	3,927 (37.0)	43,197 (37.0)
Female	66,750 (63.0)	6,675 (63.0)	73,425 (63.0)
Age, years			
Median (IQR)	29.8 (22.6-44.8)	29.8 (22.6-44.8)	29.8 (22.6-44.8)
Mean (+/- SD)	34.6 (15.0)	34.6 (15.0)	34.6 (15.0)
18-19, n (%)	12,220 (11.5)	1,222 (11.5)	13,442 (11.5)
20-29, n (%)	41,050 (38.7)	4,105 (38.7)	45,155 (38.7)
30-39, n (%)	21,490 (20.3)	2,149 (20.3)	23,639 (20.3)
40-49, n (%)	14,020 (13.2)	1,402 (13.2)	15,422 (13.2)
50-59, n (%)	8,930 (8.4)	893 (8.4)	9,823 (8.4)
60-69, n (%)	4,700 (4.4)	470 (4.4)	5,170 (4.4)
70-79, n (%)	2,530 (2.4)	253 (2.4)	2,783 (2.4)
≥80, n (%)	1,080 (1.0)	108 (1.0)	1,188 (1.0)
Age group			
18 - <40 y, n (%)	74,760 (70.5)	7,476 (70.5)	82,236 (70.5)
>40 y, n (%)	31,260 (29.5)	3,126 (29.5)	34,386 (29.5)
History of hospital diagnosed asthma†, n (%)	516 (0.5)	455 (4.3)	971 (0.8)
History of hospital diagnosed hay fever‡, n (%)	136 (0.1)	250 (2.36)	386 (0.3)
Charlson comorbidity index§,l, n (%)			
0	102,956 (97.1)	10,130 (95.5)	113,086 (97.0)
1	1,563 (1.5)	230 (2.2)	1,793 (1.5)
2	989 (0.9)	153 (1.4)	1,142 (1.0)
>2	512 (0.5)	89 (0.8)	601 (0.5)
Socioeconomic status, n (%)**			
Lowest	21,168 (19.9)	2,157 (20.3)	23,325 (20.0)
Below average	21,094 (19.9)	2,230 (21.0)	23,324 (20.0)
Average	21,131 (20.0)	2,093 (19.7)	23,324 (20.0)
Above average	21,390 (20.2)	1,935 (18.3)	23,325 (20.0)
Highest	21,137 (19.9)	2,187 (20.6)	23,324 (20.0)

Abbreviations: N, number of adult patients; IQR, interquartile range; SD, standard deviation.

* Atopic dermatitis made by a dermatologist, using the diagnostic J20 code of the International Classification of Diseases 10th revision

† Asthma defined using the diagnostic J45-J46 codes of the International Classification of Diseases 10th revision and within the 2 years before the index date

‡ Hay fever defined using the diagnostic J30 code of the International Classification of Diseases 10th revision and within the 2 years before the index date

§ recorded over seven years before the index date using the SAS macro for use of the Charlson comorbidity index with Electronic Health Care database (Thyssen et al., 2017)

l Age-adjusted Charlson index

** Divided into age-standardized quintiles

Table 2: Absolute incidence rates, incidence rate difference, population attributable risk of systemic infections

	Absolute incidence rates among the general population per 10,000 person-years (95%CI)	Absolute incidence rates among the AD population per 10,000 person-years (95%CI)	Incidence rate difference per 10,000 person-years (95%CI)	Incidence difference ratio (95%CI)	Attributable fraction among the AD population (95%CI)	Attributable fraction among the total population
Systemic infections*						
All	120.41 (118.35-122.49)	180.66 (172.66-189.02)	60.25 (51.81-68.68)	1.50 (1.43-1.57)	0.33 (0.30-0.36)	0.14
Upper respiratory tract infections	7.72 (7.23-8.25)	11.26 (9.48-13.38)	3.54 (1.53-5.55)	1.45 (1.20-1.75)	0.31 (0.17-0.43)	0.03
Lower respiratory tract infections	33.67 (32.62-34.75)	58.03 (53.74-62.67)	24.36 (19.77-28.95)	1.72 (1.58-1.87)	0.42 (0.37-0.46)	0.06
Gastrointestinal tract infections	38.38 (37.26-39.55)	46.39 (42.57-50.55)	8.00 (3.85-12.15)	1.20 (1.10-1.32)	0.17 (0.09-0.24)	0.01
Urinary tract infections	29.17 (28.20-30.18)	32.06 (28.92-35.53)	2.88 (-0.55-6.33)	1.09 (0.98-1.22)	0.09 (-0.01-0.18)	0.008
Musculoskeletal tract infections	4.14 (3.78-4.53)	8.98 (7.40-10.90)	4.84 (3.07-6.61)	2.17 (1.73-2.69)	0.53 (0.42-0.62)	0.09
Nervous system infections	1.81 (1.58-2.07)	2.77 (1.96-3.92)	0.96 (0.02-1.96)	1.53 (1.02-2.23)	0.34 (0.02-0.55)	0.04
Heart infections	1.85 (1.62-2.12)	3.65 (2.70-4.94)	1.79 (0.66-2.93)	1.96 (1.37-2.75)	0.49 (0.27-0.63)	0.08
Sepsis	8.27 (7.76-8.81)	13.77 (11.79-16.10)	5.50 (3.30-7.72)	1.60 (1.40-1.97)	0.40 (0.28-0.49)	0.05
Skin infections	11.46 (10.86-12.10)	32.37 (29.22-35.86)	20.91 (17.54-24.28)	2.82 (2.51-3.17)	0.64 (0.60-0.68)	0.14
Herpes infections*	0.64 (0.51-0.80)	3.82 (2.84-5.14)	3.18 (2.04-4.32)	5.97 (4.01-8.78)	0.83 (0.75-0.88)	0.31
Staphylococcal infections*	5.92 (5.49-6.38)	14.74 (12.67-17.14)	8.82 (6.55-11.09)	2.48 (2.09-2.95)	0.59 (0.52-0.66)	0.11

Abbreviations: AD, Atopic Dermatitis; CI, confidence interval

* Categories of infection defined using the diagnostic codes of the International Classification of Diseases 10th revision listed in Supplemental Table 2.

Table 3: Association between atopic dermatitis and systemic infections (first infection)

	Patient years at risk	Number of events*	Hazard ratio (95%CI) Crude	p-value	Hazard ratio (95%CI) Adjusted†	p-value
Systemic infections‡						
All						
Reference adults	1,078,576	12,987	1.00 (Ref)		1.00 (Ref)	
AD adults	103,787	1,875	1.51 (1.44-1.58)	<0.0001	1.26 (1.19-1.33)	<0.0001
Upper respiratory tract infections						
Reference adults	1,150,085	888	1.00 (Ref)		1.00 (Ref)	
AD adults	114,523	129	1.46 (1.21-1.76)	<0.0001	1.42 (1.15-1.73)	<0.0001
Lower respiratory tract infections						
Reference adults	1,137,583	3,830	1.00 (Ref)		1.00 (Ref)	
AD adults	111,831	649	1.73 (1.59-1.88)	<0.0001	1.21 (1.10-1.33)	<0.0001
Gastrointestinal tract infections						
Reference adults	1,128,221	4,331	1.00 (Ref)		1.00 (Ref)	
AD adults	112,088	520	1.21 (1.10-1.32)	<0.0001	1.03 (0.93-1.14)	0.577
Urinary tract infections						
Reference adults	1,136,986	3,317	1.00 (Ref)		1.00 (Ref)	
AD adults	113,230	363	1.10 (0.99-1.20)	0.087	0.99 (0.88-1.11)	0.825
Musculoskeletal tract infections						
Reference adults	1,151,933	477	1.00 (Ref)		1.00 (Ref)	
AD adults	114,659	103	2.17 (1.75-2.68)	<0.0001	1.81 (1.42-2.31)	<0.0001
Nervous system infections						
Reference adults	1,154,515	209	1.00 (Ref)		1.00 (Ref)	
AD adults	115,160	32	1.53 (1.06-2.23)	0.002	1.12 (0.74-1.72)	0.585
Heart infections						
Reference adults	1,154,324	214	1.00 (Ref)		1.00 (Ref)	
AD adults	115,039	42	1.97 (1.41-2.74)	<0.0001	1.75 (1.21-2.53)	0.003
Sepsis						
Reference adults	1,152,732	953	1.00 (Ref)		1.00 (Ref)	
AD adults	114,696	158	1.67 (1.41-1.97)	<0.0001	1.19 (1.01-1.44)	0.050
Skin infections						
Reference adults	1,147,376	1,315	1.00 (Ref)		1.00 (Ref)	
AD adults	113,064	366	2.83 (2.52-3.18)	<0.0001	2.30 (2.01-2.62)	<0.0001

Herpes infections[‡]						
Reference adults	1,155,223	74	1.00 (Ref)		1.00 (Ref)	
AD adults	115,062	44	5.97 (4.11-8.67)	<0.0001	5.28 (3.47-8.02)	<0.0001
Staphylococcal infections[‡]						
Reference adults	1,150,129	681	1.00 (Ref)		1.00 (Ref)	
AD adults	113,970	168	2.48 (2.10-2.95)	<0.0001	2.11 (1.75-2.56)	<0.0001

Abbreviations: N, number of patients; CI, confidence interval; Ref, reference

[*] Number of first infections during study period (to count from the index date which is the date of the diagnosis of atopic dermatitis)
[†] Adjusted on age, atopic comorbidities (asthma and/or hay fever, time-updated variables), socioeconomic level (at the index date), smoking and alcohol (ever, yes/no), Charlson comorbidity index (at the index date) and immunosuppressant treatment (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, time-updated variable)
[‡] Categories of infection defined using the diagnostic codes of the International Classification of Diseases 10th revision listed in Supplemental Table 1.

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Figure legend

Figure 1: Flow chart

Abbreviations: AD, atopic dermatitis; N, number of individuals

[a] Atopic dermatitis diagnosis defined using the diagnostic L20 code of the International Classification of Diseases 10th revision and made by a dermatologist

[b] Atopic dermatitis diagnosis defined using the diagnostic L20 code of the International Classification of Diseases 10th revision and made by a dermatologist and/ or a pediatrician

Figure 2: Association between atopic dermatitis and systemic infections (first infection, crude and adjusted models)

Abbreviations: HR, Hazard ratios; CI, confidence interval

Adjusted on age, atopic comorbidities (asthma and/or hay fever, time-updated variables), socioeconomic level (at the index date), smoking and alcohol (ever yes/no), Charlson comorbidity index (at the index date), immunosuppressant treatment (time-updated variable)

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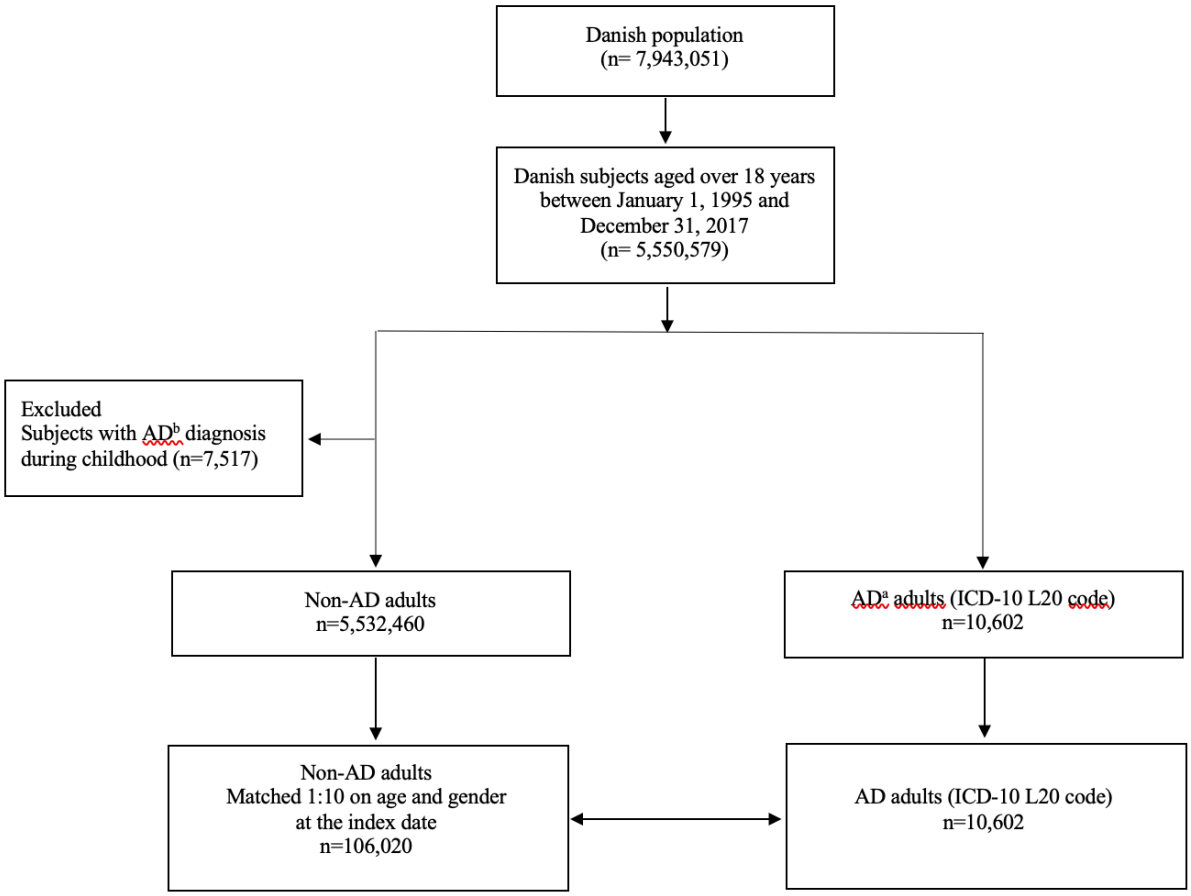
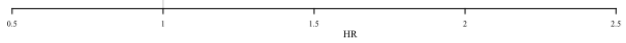

Danish population
(n= 7,943,051)
Danish subjects aged over 18 years between January 1, 1995 and December 31, 2017
(n= 5,550,579)
Excluded
Subjects with AD[b] diagnosis during childhood (n=7,517)
Non-AD adults
n=5,532,460
AD[a] adults (ICD-10 L20 code)
n=10,602
Non-AD adults
Matched 1:10 on age and gender at the index date
n=106,020
AD adults (ICD-10 L20 code)
n=10,602

Infections	HR (CI95%)
Upper respiratory tract	
Crude	1.46 (1.21; 1.76)
Adjusted	1.42 (1.15; 1.73)
Lower respiratory tract	
Crude	1.73 (1.59; 1.88)
Adjusted	1.21 (1.10; 1.33)
Gastrointestinal tract	
Crude	1.21 (1.10; 1.32)
Adjusted	1.03 (0.93; 1.14)
Urinary tract	
Crude	1.10 (0.99; 1.20)
Adjusted	0.99 (0.88; 1.11)
Musculoskeletal system	
Crude	2.17 (1.75; 2.68)
Adjusted	1.81 (1.42; 2.31)
Nervous system	
Crude	1.53 (1.06; 2.23)
Adjusted	1.12 (0.74; 1.72)
Heart	
Crude	1.97 (1.41; 2.74)
Adjusted	1.75 (1.21; 2.53)
Sepsis	
Crude	1.67 (1.41; 1.97)
Adjusted	1.19 (1.01; 1.44)



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