

Increased all-cause mortality in concomitant atopic dermatitis and asthma: A nationwide registry-based study

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Abstract

Background: Excess mortality has been reported for adults with atopic dermatitis (AD) and asthma.

Objective: To assess the mortality rate in adults with concomitant AD and asthma.

Methods: Adults with hospital-diagnosed AD were matched (1:4) with non-AD individuals from the background population.

Results: The study cohort comprised 8,095 adults with AD (of which 1,201 (14.8%) had concomitant asthma) and 32,380 reference individuals without AD from the background population (of which 878 (2.7%) had asthma). A total of 1,057, 330, 55 and 99 deaths were observed among subjects with neither AD nor asthma, AD only, asthma only, and subjects with concomitant AD and asthma, respectively. The mortality rate per 1,000 person-years was 4.75 (95% CI 4.47–5.05) for subjects with neither AD nor asthma, 7.17 (95% CI 5.92–10.05) for asthma only, 7.09 (95% CI 6.37–7.90) for AD only and 10.87 (95% CI 8.92–13.23) for concomitant AD and asthma. Risk for all-cause mortality was increased in subjects with concomitant AD and asthma compared to asthma only (HR 1.52, 95% CI 1.07–2.15) and neither AD nor asthma (HR 2.27, 95% CI 1.83–2.81) but not compared to subjects with AD only (HR 1.10, 95% CI 0.87–1.39). However, compared to AD only subjects with AD and asthma had increased risk of death due to pulmonary disease (HR 1.81, 95% CI 1.04–3.15).

Conclusion: Adults with AD, asthma or both conditions have increased risk of death, and further concomitant AD and asthma have increased risk of death compared with asthma alone.

KEYWORDS

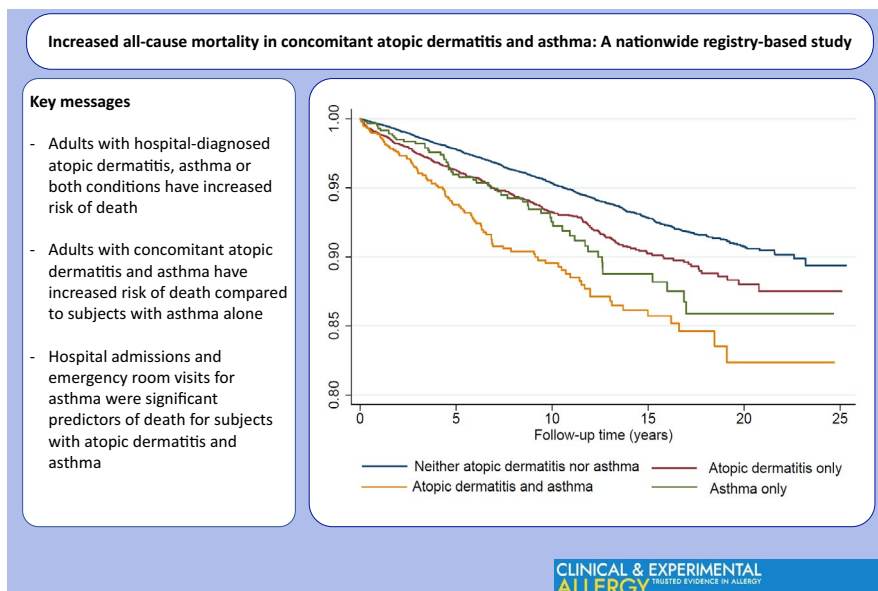
asthma, atopic dermatitis, eczema, mortality

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic and inflammatory skin disease, ranked highest with respect to disability-adjusted life-years and years lived with a disease.¹ The prevalence of AD in adults ranges from 2% to 5%.² Asthma is a chronic airway disease with a significant impact on quality of life.³ The prevalence of asthma in adults

is around 8%.⁴ Overwhelming evidence supports a causal link between occurrence of asthma and AD.⁵ The prevalence of asthma among patients with AD is reported to be as high as 25%.⁶

Adults with AD have a higher risk for death from cardiovascular and infectious diseases.⁷ Further, the mortality is higher after hospitalization for AD compared with reference individuals from the general population.⁸ Moreover, adults with asthma also have an excess



GRAPHICAL ABSTRACT

- Adults with hospital-diagnosed atopic dermatitis, asthma or both conditions have increased risk of death.
- Adults with concomitant atopic dermatitis and asthma have increased risk of death compared to subjects with asthma alone.
- Hospital admissions and emergency room visits for asthma were significant predictors of death for subjects with atopic dermatitis and asthma.

mortality that to a large extent can be explained by death from lung diseases.⁹ In recent decades, mortality from asthma has declined worldwide; nevertheless, the number of asthmatic patients dying is still disturbingly high.¹⁰

Although the significant association between asthma and AD is well known, data on excess mortality in these patients have, to the best of our knowledge, never been studied. Obtaining knowledge here will provide a valuable measure for assessing health status in patients with concomitant AD and asthma and may be an important indicator of potential to improve the health status as many deaths are preventable. The aim of this study was to determine the mortality rate in patients with hospital-diagnosed concomitant AD and asthma compared to patients with AD only, asthma only and to the background population without these diseases, further, to examine the impact of healthcare utilization for AD and asthma on mortality rate.

2 | METHODS

2.1 | Data sources

The Danish National Patient Registry¹¹ contains prospectively collected data on diagnoses from all hospital admissions and outpatient contacts at all Danish hospitals and from a number of private clinics, since 1978 using the International Classification of Diseases (ICD) codes (since 1994 according to the ICD-10 classification). The National Causes of Death Registry contains information on primary and contributing causes of death obtained from official death certificates, and registration is mandatory by law.¹² Data on all pharmacy-dispensed medications are recorded in the Danish Registry of Medicinal Products

Key Messages

- Adults with atopic dermatitis, asthma or both conditions have increased risk of death
- Concomitant atopic dermatitis and asthma have increased risk of death compared with asthma alone.
- It is unknown whether the increased risk of death is due to disease severity.

Statistics,¹³ information on tax-reported household income is recorded by Statistics Denmark,¹⁴ and information on age, sex, vital and migration status is recorded in the Civil Registration System (CPR).¹⁵ The unique personal identification number, which is assigned to each Danish citizen at birth or immigration, enabled individual-level linkage across nationwide administrative registries.¹⁵

2.2 | Study population

All Danes aged ≥ 18 years from 1 January 1997 onwards were identified from the CPR number. Patients with two hospital diagnoses of AD (ICD-10 L20) with an interval of at least 6 months between the two were defined as having AD. Cohort entry (index) was defined as the time of the last of the two AD diagnoses. Asthma was defined as diagnosis of asthma (ICD-10 J45), and at least two filled prescriptions of inhaled corticosteroids. The diagnostic code for AD and asthma has been validated in Danish registries.^{16,17} All individuals were followed from the age of 18 and were included as AD subjects at the

time of the last of the two AD diagnoses. Individuals were followed until migration, death or 31 December 2018 whichever came first.

Subjects with AD were individually age (at index) and sex-matched with the background population of individuals without a diagnosis of AD in a 1:4 ratio. Individuals subsequently diagnosed with AD were not available for matching prior to AD diagnosis. (Figure S1).

2.3 | Definition

The primary cause of death from the National Causes of Death Register was classified into the following categories: infectious diseases, neoplasms, endocrine, psychiatric, neurologic, cardiovascular, pulmonary, gastrointestinal and hepatic, urogenital diseases and other diseases including diseases of the blood and blood-forming organs, diseases of the eye and adnexa, diseases of the ear and mastoid process, diseases of the skin and subcutaneous tissue and diseases of the musculoskeletal system and connective tissue.

Systemic corticosteroid prescriptions regardless of duration and indication, hospital admissions for atopic dermatitis, and emergency room visits and hospital admissions for asthma have been used as predictors of mortality.

Socio-economic status was calculated as an age-standardized index (quintiles) based on the mean annual income in the last 5 years before study start (Table S1 includes all codes used in the study).

2.4 | Statistics

Descriptive characteristics were reported as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Age was divided into 10-year age bands. The incidence rates (IR) per 1000 person-years of all-cause mortality and cause-specific mortality were calculated, and crude and adjusted (age, sex, socio-economic status and education level at baseline) (Figure S2) hazard ratios (HRs) were estimated with a Cox regression model. The *p*-value of <.05 was considered statistically significant, and results were reported with 95% confidence intervals (CIs), where applicable. Data on one or two individuals are not shown, due to data security requirements.

A complete-case analysis was carried out as a sensitivity analysis as educational level was missing for 437 subjects (1%). There were no missing data for age, sex, socio-economic status or any other variable.

All analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC) and STATA software, version 13.0 (StataCorp, College Station, TX).

2.5 | Ethics

The study was approved by the Danish Data Protection Agency. In Denmark, register studies do not require ethical approval.

3 | RESULTS

The study cohort comprised a total of 8,095 subjects (61.8% females) with hospital-diagnosed AD of which 1,201 (15%) had concomitant asthma; 32,380 matched subjects without AD from the background population of which 878 (3%) had asthma (Characteristics of participants with atopic dermatitis and background population are given in Table S2). The mean age at death was highest in subjects with neither AD nor asthma (73.32) compared to subjects with AD only (69.28), concomitant AD and asthma (69.61), and asthma only (72.07). Subjects with asthma only (8%) and subjects with concomitant AD and asthma (7%) had fewer in the lowest socio-economic status group compared to subjects with AD only (22%) and neither AD nor asthma (20%). Subjects with concomitant AD and asthma were more often admitted to hospital for asthma (25%) and for AD (13%) compared to subjects with asthma only (17%) or AD only (8%). Further, they also had more prescriptions of systemic corticosteroids (66%) compared to subjects with AD only (33%) and asthma only (40%) (Table 1).

3.1 | Mortality

During follow-up, a total of 1,057 (524 males and 533 females), 330 (174 males and 156 females), 55 (21 males and 34 females) and 99 (54 males and 45 females) deaths were observed among subjects with neither AD nor asthma, subjects with AD only, subjects with asthma only and subjects with concomitant AD and asthma, respectively (Table 2). Even though around 60% of subjects with AD only, and concomitant AD and asthma were women, 54.5% of males died among those with concomitant AD and asthma compared to 49.5% in subjects with neither AD nor asthma, 38.2% in subjects with asthma only, and 52.7% in subjects with AD only. The mean age at death was lower in subjects with concomitant AD and asthma compared to subjects with neither AD nor asthma and subjects with asthma only. However, the mean age at death was similar among subjects with AD only, and concomitant AD and asthma. Risk of all-cause mortality in men compared to women in the four groups is visualized in Figure 1.

The two most frequent causes of death were cardiovascular disease (26.9%, 22.1% and 23.2%) and cancer (35.5%, 30.3% and 32.3%) in subjects with neither AD nor asthma, subjects with AD only, and subjects with concomitant AD and asthma, respectively. In subjects with asthma only, pulmonary disease (38.2%) and cancer (34.5%) were the most frequent causes of death, whereas cardiovascular disease was the only cause of death in 14.5% (Table 2). The all-cause mortality rate given in incidence rates per 1,000 person-years was 4.75 (95% CI 4.47–5.05) for subjects with neither AD nor asthma, 7.17 (95% CI 5.92–10.05) for asthma only, 7.09 (95% CI 6.37–7.90) for AD only and 10.87 (95% CI 8.92–13.23) for concomitant AD and asthma, thus highest for subjects with concomitant AD and asthma. Kaplan-Meier survival curve is visualized in Figure 2, showing that the mortality risk is highest for subjects with concomitant AD and asthma. The risk of all-cause mortality was significantly

TABLE 1 Characteristics of the study population

Characteristics	Atopic dermatitis and asthma	Atopic dermatitis only	Asthma only	Neither atopic dermatitis nor asthma
Number	1,201	6,894	878	31,502
Sex, n (%)				
Men	472 (39.3)	2,620 (38.0)	271 (30.9)	12,097 (38.4)
Women	729 (60.7)	4,274 (62.0)	607 (69.1)	19,405 (61.6)
Age at death, years				
Mean SD	69.61 (13.5)	69.28 (15.1)	72.07 (14.2)	73.32 (15.1)
Socio-economic status, n (%)				
Lowest	93 (7.7)	1,533 (22.2)	71 (8.1)	6,398 (20.3)
Below average	259 (21.6)	1,386 (20.1)	201 (22.9)	6,249 (19.8)
Average	293 (24.4)	1,318 (19.1)	245 (27.9)	6,239 (19.8)
Above average	284 (23.7)	1,265 (18.3)	194 (22.1)	6,352 (20.2)
Highest	272 (22.7)	1,392 (20.2)	167 (19.0)	6,264 (19.9)
Education level, n (%)				
Primary school	265 (22.1)	1,240 (17.9)	249 (28.4)	6,488 (20.6)
High/ vocational school	495 (41.2)	2,904 (42.2)	349 (39.7)	13,669 (43.4)
Short and medium	310 (25.8)	1,838 (26.7)	208 (23.7)	7,723 (24.5)
Higher	121 (10.1)	855 (12.4)	62 (7.1)	3,273 (10.4)
Hospital admission for atopic dermatitis				
n (%)	159 (13.2)	606 (8.8)		
Hospital admission for asthma				
n (%)	304 (25.3)		152 (17.3)	
Mean (SD)	3.47 (5.7)		1.91 (2.1)	
Emergency room visit for asthma				
n (%)	48 (4.0)		31 (3.5)	
Mean (SD)	1.52 (1.7)		1.37 (0.8)	
Systemic corticosteroids				
n (%)	801 (66.7)	2,317 (33.6)	357 (40.7)	2,610 (8.3)
Mean (SD)	11.39 (20.2)	6.42 (13.9)	8.10 (14.3)	4.47 (10.1)

Abbreviations: AD, atopic dermatitis, SD, standard deviation.

increased in subjects with AD only compared to subjects with neither AD nor asthma ($HR_{\text{adjusted}} 1.94$, 95% CI 1.71–2.21), subjects with concomitant AD and asthma compared to subjects with asthma only ($HR_{\text{adjusted}} 1.52$, 95% CI 1.07–2.15), and subjects with concomitant AD and asthma compared to subjects with neither AD nor asthma ($HR_{\text{adjusted}} 2.27$, 95% CI 1.83–2.81) (Table 3). Further, subjects with AD and asthma had increased risk of death due to pulmonary disease compared to AD only ($HR_{\text{adjusted}} 1.81$, 95% CI 1.04–3.15), and subjects with neither AD nor asthma ($HR_{\text{adjusted}} 5.03$, 95% CI 3.05–8.29). (Table 3).

Additionally, subjects with concomitant AD and asthma also had higher risk of cardiovascular death compared to subjects with neither AD nor asthma ($HR_{\text{adjusted}} 2.07$ [95% CI 1.32–3.24]). Likewise, subjects with AD only also had increased risk of cardiovascular death compared to subjects with neither AD nor asthma (HR_{adjusted}

1.71 [95% CI 1.29–2.24]; however, this was not the case for asthma only ($HR_{\text{adjusted}} 0.78$ [95% CI 0.37–1.66]).

Further, subjects with AD and asthma had higher risk of death due to psychiatric diseases compared to neither AD nor asthma ($HR_{\text{adjusted}} 2.54$ [95% CI 1.08–5.96]) even though the risk was not increased for subjects with AD or asthma alone.

3.2 | Impact of healthcare utilization for atopic dermatitis and asthma on mortality

Emergency room visits for asthma were not a predictor of death for subjects with asthma only ($HR_{\text{adjusted}} 1.53$ [95% CI 0.71–3.33]); however, it was a predictor for subjects with AD and asthma ($HR_{\text{adjusted}} 1.69$ [95% CI 1.06–2.67]). Hospital admission for AD was

TABLE 2 Mortality among subjects with concomitant atopic dermatitis and asthma, atopic dermatitis only, asthma only, and neither atopic dermatitis nor asthma, by cause of death

Cause of death	Atopic dermatitis and asthma	Atopic dermatitis only	Asthma only	Neither atopic dermatitis nor asthma
All-cause mortality				
Events (n)	99	330	55	1,057
IR (95% CI)	10.87 (8.92–13.23)	7.09 (6.37–7.90)	7.17 (5.92–10.05)	4.75 (4.47–5.05)
Pulmonary disease				
Events (n)	20	41	21	105
IR (95% CI)	2.19 (1.42–3.40)	0.88 (0.65–1.19)	2.95 (1.19–4.52)	0.47 (0.38–0.57)
Cardiovascular disease				
Events (n)	23	73	8	285
IR (95% CI)	2.52 (1.68–3.80)	1.57 (1.24–1.97)	1.22 (0.56–2.24)	1.28 (1.14–1.44)
Neoplasm/cancer				
Events (n)	32	100	19	376
IR (95% CI)	3.51 (2.48–4.97)	2.15 (1.76–2.61)	2.67 (1.67–4.18)	1.69 (1.52–1.87)
Infectious disease				
Events (n)	<3	9	<3	20
IR (95% CI)	0.23 (0.05–0.88)	0.19 (0.10–0.37)	0.14 (0.02–1.00)	0.09 (0.06–0.14)
Endocrine disease				
Events (n)	<3	14	<3	39
IR (95% CI)	0.22 (0.05–0.88)	0.30 (0.18–0.51)	0.28 (0.07–1.12)	0.18 (0.13–0.24)
Gastrointestinal disease				
Events (n)	8	32	<3	48
IR (95% CI)	0.88 (0.44–1.76)	0.68 (0.48–0.97)	0.14 (0.02–1.00)	0.22 (0.16–0.28)
Neurologic disease				
Events (n)	<3	15	0	32
IR (95% CI)	0.22 (0.05–0.88)	0.32 (0.19–0.53)	-	0.14 (0.10–0.20)
Urogenital disease				
Events (n)	<3	<3	<3	16
IR (95% CI)	0.12 (0.02–0.78)	0.04 (0.01–0.17)	0.14 (0.02–0.99)	0.07 (0.04–0.12)
Psychiatric disease				
Events (n)	6	19	<3	70
IR (95% CI)	0.67 (0.30–1.47)	0.40 (0.26–0.64)	0.14 (0.02–1.00)	0.31 (0.25–0.39)
Other diseases				
Events (n)	<3	3	0	22
IR (95% CI)	0.22 (0.05–0.88)	0.06 (0.02–0.20)	-	0.09 (0.06–0.15)

Abbreviations: CI, confidence interval; IR, incidence rates per 1,000 person-years.

Data on one or two individuals are shown as <3, due to data security requirements.

a significant predictor for all-cause mortality for subjects with AD only (HR_{adjusted} 1.77 [95% CI 1.35–2.31]) but not for subjects with AD and asthma (HR_{adjusted} 1.43 [95% CI 0.85–2.42]). Hospital admission for asthma was a significant predictor of death in a dose-dependent manner for both subjects with asthma only and subjects with AD and asthma. Treatment with systemic corticosteroid was a predictor of all-cause mortality for AD subjects and subjects with neither AD nor asthma in a dose-dependent manner. These results were not found for subjects with asthma only and subjects with AD and asthma. (Table 4).

Repeating the analyses after exclusion of all missing data did not change the overall results (Tables S3–S5).

4 | DISCUSSION

In the present study, adults with hospital-diagnosed concomitant AD and asthma had higher risk of all-cause mortality compared to adults with asthma only but not compared to adults with AD only. Further, hospital admission for asthma, and asthma-related emergency room

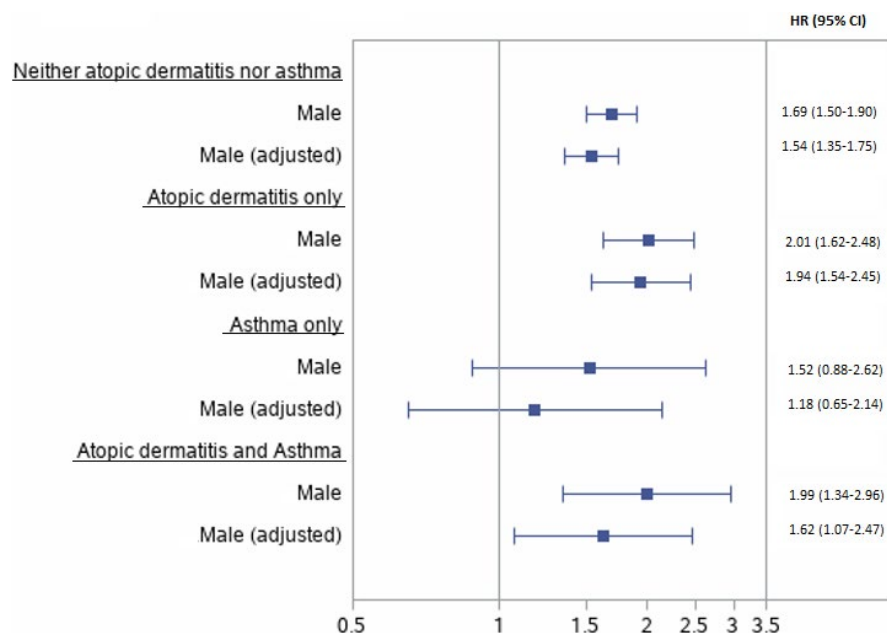


FIGURE 1 Risk of all-cause mortality in men compared to women among subjects with atopic dermatitis only, asthma only, concomitant atopic dermatitis and asthma, and neither atopic dermatitis nor asthma. Abbreviations: HR, hazard ratio; CI, confidence interval. Adjusted for age, socio-economic status and educational level

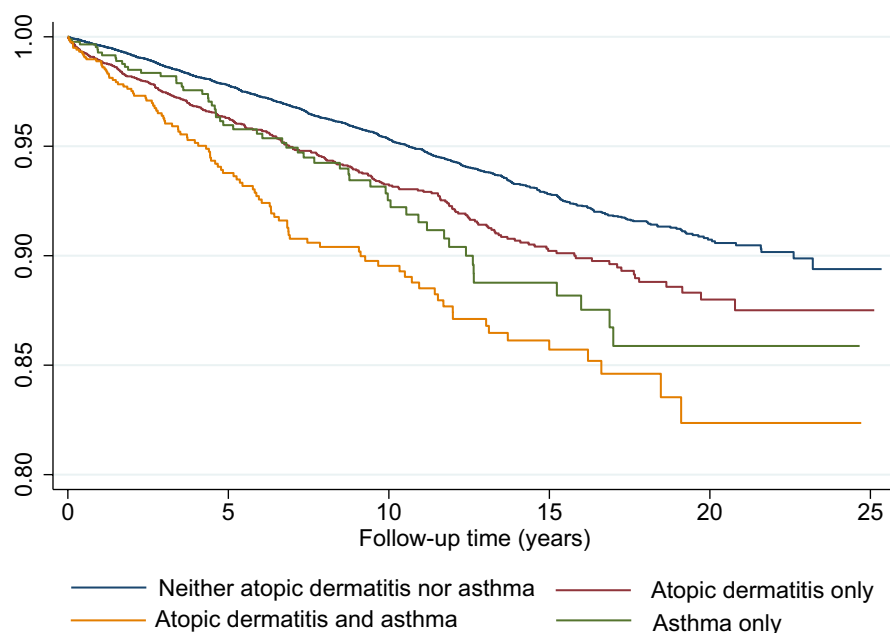


FIGURE 2 Kaplan-Meier survival curves for time to all-cause mortality for subjects with neither atopic dermatitis nor asthma, atopic dermatitis only, asthma only, and subjects with concomitant atopic dermatitis and asthma. Y-axis does not start at zero

visits and hospital admission for AD were significant predictors of death in adults with concomitant AD and asthma.

Men had increased risk of death in all four groups, though not statistically significant for subjects with asthma only. The results are in line with previous literature, showing that men have higher mortality compared with women.¹⁸ This is partly explained by differential healthcare usage,¹⁸ and social and behavioural differences, such as alcohol consumption and smoking patterns.¹⁹ Men with AD, and concomitant AD and asthma had higher risk of death than subjects with neither AD nor asthma in our study. Increased risk of cigarette smoking has been observed in AD^{20,21} and asthma²² populations, and this could explain the excessive mortality.

Adults with concomitant AD and asthma had increased risk of death and death due to cardiovascular disease compared to adults with asthma only. Though, increased risk of death due to cardiovascular disease did not remain significant after adjusting for confounders. Cardiovascular outcomes including angina, myocardial infarction and heart failure are common in patients with AD^{23,24} and are also reflected in increased cardiovascular mortality.⁷ Mortality in patients with asthma is also significantly increased mainly due to pulmonary diseases,²⁵ and this was reflected in that subjects with concomitant AD and asthma had significantly increased mortality due to pulmonary disease compared to subjects with AD only. In the context of increased death due to psychiatric diseases for subjects with concomitant AD and asthma, future studies should investigate

TABLE 3 The risk for cause-specific mortality

Cause of death	Atopic dermatitis only vs neither atopic asthma	Asthma only vs neither atopic dermatitis nor asthma	Atopic dermatitis and asthma vs atopic dermatitis only	Atopic dermatitis and asthma vs asthma only	Atopic dermatitis and asthma vs neither atopic dermatitis nor asthma
All-cause mortality					
HR (95% CI)	2.15 (1.65–2.78)	1.61 (1.23–2.11)	1.55 (1.24–1.94)	1.40 (1.01–1.95)	2.28 (1.85–2.80)
p-value	p < .001	p < .001	p < .001	p = .045	p < .001
HR _{adjusted} (95% CI)	1.94 (1.71–2.21)	1.45 (1.09–1.91)	1.10 (0.87–1.39)	1.52 (1.07–2.15)	2.27 (1.83–2.81)
p-value	p < .001	p = .009	p = .433	p = .019	p < .001
Pulmonary disease					
HR (95% CI)	1.87 (1.31–2.68)	6.16 (3.85–6.84)	2.53 (1.48–4.32)	0.74 (0.40–1.37)	4.65 (2.88–7.50)
p-value	p = .001	p < .001	p = .001	p = .335	p < .001
HR _{adjusted} (95% CI)	2.56 (1.75–3.72)	5.61 (3.46–9.11)	1.81 (1.04–3.15)	0.86 (0.45–1.66)	5.03 (3.05–8.29)
p-value	p < .001	p < .001	p = .037	p = .661	p < .001
Cardiovascular disease					
HR (95% CI)	1.22 (0.94–1.58)	0.87 (0.43–1.76)	1.64 (1.03–2.63)	2.22 (1.00–4.97)	1.96 (1.28–3.01)
p-value	p = .124	p = .709	p = .038	p = .052	p = .002
HR _{adjusted} (95% CI)	1.71 (1.29–2.24)	0.78 (0.37–1.66)	1.14 (0.69–1.88)	2.87 (1.19–6.95)	2.07 (1.32–3.24)
p-value	p < .001	p = .528	p = .599	p = .102	p = .001
Neoplasm/cancer					
HR (95% CI)	1.27 (1.02–1.58)	1.57 (0.99–2.49)	1.65 (1.11–2.45)	1.32 (0.75–2.33)	2.07 (1.44–2.97)
p-value	p = .032	p = .055	p = .014	p = .339	p < .001
HR _{adjusted} (95% CI)	1.52 (1.21–1.90)	1.36 (0.86–2.16)	1.16 (0.77–1.75)	1.22 (0.68–2.17)	1.85 (1.27–2.69)
p-value	p < .001	p = .187	p = .482	p = .511	p = .001
Infectious disease					
HR (95% CI)	2.15 (0.97–4.72)	1.56 (0.21–11.61)	1.17 (0.25–5.44)	1.56 (0.14–17.24)	2.44 (0.57–10.47)
p-value	p = .056	p = .665	p = .837	p = .716	p = .227
HR _{adjusted} (95% CI)	2.51 (1.07–5.86)	1.40 (0.18–10.61)	0.97 (0.20–4.67)	1.92 (0.16–23.12)	2.76 (0.62–12.16)
p-value	p = .033	p = .774	p = .972	p = .606	p = .178
Endocrine disease					
HR (95% CI)	1.70 (0.92–3.13)	1.62 (0.39–6.73)	0.76 (0.17–3.34)	0.78 (0.11–5.53)	1.26 (0.30–5.22)
p-value	p = .088	p = .504	p = .714	p = .803	p = .750
HR _{adjusted} (95% CI)	2.25 (1.22–4.16)	1.41 (0.34–5.87)	0.54 (0.12–2.39)	1.12 (0.14–9.03)	1.16 (0.27–4.83)
p-value	p = .010	p = .634	p = .415	p = .915	p = .840

(Continues)

TABLE 3 (Continued)

Cause of death	Atopic dermatitis only vs neither atopic dermatitis nor asthma	Asthma only vs neither atopic dermatitis nor asthma	Atopic dermatitis and asthma vs atopic dermatitis only	Atopic dermatitis and asthma vs asthma only	Atopic dermatitis and asthma vs neither atopic dermatitis nor asthma
Gastrointestinal disease					
HR (95% CI)	3.19 (2.04–4.99)	0.64 (0.08–4.65)	1.29 (0.59–2.81)	6.21 (0.78–49.62)	4.04 (1.91–8.55)
p-value	p < .001	p = .660	p = .515	p = .085	p < .001
HR _{adjusted} (95% CI)	4.09 (2.58–6.46)	0.57 (0.08–4.11)	0.71 (0.31–1.63)	6.11 (0.74–50.72)	3.30 (1.47–7.38)
p-value	p < .001	p = .575	p = .422	p = .094	p = .004
Neurologic disease					
HR (95% CI)	2.26 (1.22–4.17)		0.65 (0.15–2.85)		1.49 (0.35–6.23)
p-value	p = .009		p = .569		p = .582
HR _{adjusted} (95% CI)	3.14 (1.68–5.87)		0.44 (0.09–1.96)		1.42 (0.33–6.09)
p-value	p < .001		p = .281		p = .630
Urogenital disease					
HR (95% CI)	0.59 (0.14–2.59)	1.98 (0.26–14.95)	2.61 (0.24–28.79)	0.76 (0.05–12.21)	1.56 (0.21–11.73)
p-value	p = .490	p = .507	p = .434	p = .849	p = .668
HR _{adjusted} (95% CI)	0.90 (0.20–4.06)	1.85 (0.24–14.34)	3.42 (0.16–73.05)	2.81 (0.12–63.46)	1.87 (0.24–14.60)
p-value	p = .899	p = .557	p = .431	p = .516	p = .547
Psychiatric disease					
HR (95% CI)	1.30 (0.78–2.16)	0.43 (0.06–3.12)	1.68 (0.67–4.21)	4.67 (0.56–38.83)	2.06 (0.89–4.78)
p-value	p = .306	p = .407	p = .267	p = .153	p = .089
HR _{adjusted} (95% CI)	1.64 (0.94–2.88)	0.43 (0.06–3.16)	1.33 (0.51–3.46)	6.89 (0.59–80.94)	2.54 (1.08–5.96)
p-value	p = .079	p = .412	p = .554	p = .125	p = .030
Other diseases					
HR (95% CI)	0.65 (0.19–2.17)		3.59 (0.60–21.55)		2.22 (0.52–9.43)
p-value	p = .486		p = .161		p = .281
HR _{adjusted} (95% CI)	1.06 (0.30–3.63)		7.24 (0.76–68.61)		2.63 (0.60–11.51)
p-value	p = .926		p = .08		p = .197

Abbreviations: CI, confidence interval; HR, Hazard ratio.

Adjusted for sex, age, socio-economic status and educational level.

TABLE 4 Predictors of all-cause mortality

	Events (n)	IR (95% CI)	HR (95% CI), <i>p</i> -value	HR _{adjusted} (95% CI), <i>p</i> -value
Atopic dermatitis and asthma				
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	8	3.93 (1.96–7.86)	1.95 (0.89–4.25), <i>p</i> = .091	1.19 (0.51–2.75), <i>p</i> = .678
Systemic corticosteroid 1–5	31	7.72 (5.43–10.98)	4.91 (2.34–10.27), <i>p</i> < .001	1.83 (0.82–4.09), <i>p</i> = .137
Systemic corticosteroid >5	60	19.58 (15.20–25.22)		
Hospital admissions for atopic dermatitis				
Hospital admission 0	77	9.97 (7.97–12.46)	1.65 (1.03–2.66), <i>p</i> = .037	1.44 (0.85–2.42), <i>p</i> = .172
Hospital admission =1	22	15.82 (10.41–24.03)		
Emergency room visits and hospital admissions for asthma				
Emergency room visit 0	71	9.35 (7.41–11.80)	1.92 (1.24–2.97), <i>p</i> = .003	1.69 (1.06–2.67), <i>p</i> = .025
Emergency room visit ≥1	28	18.39 (12.69–26.63)		
Hospital admission 0	21	4.40 (2.87–6.75)	2.81 (1.66–4.73), <i>p</i> < .001	1.80 (1.04–3.12), <i>p</i> = .036
Hospital admission 1–3	42	12.32 (9.10–16.67)	8.68 (5.06–14.87), <i>p</i> < .001	3.03 (1.70–5.38), <i>p</i> < .001
Hospital admission >3	36	38.52 (27.78–53.90)		
Atopic dermatitis only				
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	97	4.16 (3.41–5.07)	1.79 (1.37–2.34), <i>p</i> < .001	1.49 (1.13–1.98), <i>p</i> = .004
Systemic corticosteroid 1–5	126	7.45 (6.25–8.87)	4.11 (3.11–5.40), <i>p</i> < .001	1.87 (1.39–2.51), <i>p</i> < .001
Systemic corticosteroid >5	107	17.07 (14.13–20.64)		
Hospital admissions for atopic dermatitis				
Hospital admission 0	251	6.03 (5.34–6.83)	2.47 (2.13–3.53), <i>p</i> < .001	1.76 (1.35–2.31), <i>p</i> < .001
Hospital admission =1	79	15.99 (12.82–19.93)		
Asthma only				
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	11	3.69 (2.05–6.67)	1.87 (0.90–3.92), <i>p</i> = .093	1.64 (0.75–3.59), <i>p</i> = .213
Systemic corticosteroid 1–5	20	6.99 (4.51–10.84)	4.91 (2.41–10.04), <i>p</i> < .001	1.68 (0.78–3.66), <i>p</i> = .184
Systemic corticosteroid >5	24	18.52 (12.41–27.63)		
Emergency room visits and hospital admissions for asthma				
Emergency room visit 0	46	7.54 (5.65–10.07)	1.16 (0.56–2.37), <i>p</i> = .681	1.53 (0.71–3.33), <i>p</i> = .279
Emergency room visit ≥1	9	8.69 (4.52–16.70)		
Hospital admission 0	11	2.69 (1.49–4.86)	4.85 (2.47–9.51), <i>p</i> < .001	2.45 (1.15–5.18), <i>p</i> = .019
Hospital admission 1–3	37	13.22 (9.58–18.25)	10.24 (3.96–26.45), <i>p</i> < .001	3.98 (1.37–11.53), <i>p</i> = .011
Hospital admission >3	7	27.90 (13.31–58.54)		
Not atopic dermatitis nor asthma				
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	640	3.49 (3.23–3.77)	2.54 (2.21–2.91), <i>p</i> < .001	1.68 (1.45–1.94), <i>p</i> < .001
Systemic corticosteroid 1–5	290	8.90 (7.93–9.99)	5.53 (4.57–6.69), <i>p</i> < .001	1.71 (1.39–2.08), <i>p</i> < .001
Systemic corticosteroid >5	127	19.36 (16.27–23.05)		

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate per 1,000 person-years.

Adjusted for sex, age, socio-economic status and educational level.

if the excess mortality in subjects with concomitant AD and asthma is related to aggravate type 2 inflammation due to two chronic inflammatory diseases concomitantly.

Further, the adjusted HRs for all-cause mortality were increased for AD vs. neither AD nor asthma, concomitant AD and asthma vs. asthma only, and concomitant AD and asthma vs. neither AD nor

asthma, whereas the risk of all-cause mortality was reduced for concomitant AD and asthma vs. AD only after adjusting for confounders. The magnitude of the association was underestimated in the comparison between concomitant AD and asthma vs. asthma only, if not adjusted for confounders. However, for the other comparisons, confounding resulted in an overestimated effect, if not

accounted for. Men were not significantly overrepresented in subjects with asthma only, and this might explain the overestimation before adjusting the results for gender. Likewise, the negative confounding in the group of concomitant AD and asthma vs. asthma only could be explained by the overrepresentation of subjects from higher socio-economic status in the group of concomitant AD and asthma.

In general, the cause-specific mortalities were not significant for subjects with concomitant AD and asthma compared to subjects with AD only or asthma only besides pulmonary diseases, and other diseases including diseases of the blood-forming organs, eye, ear and skin. For gastrointestinal diseases (AD and asthma vs. asthma only: $HR_{adjusted}$ 6.11 [95% CI 0.74–50.72]) and other diseases (AD and asthma vs. AD only: $HR_{adjusted}$ 7.24 [95% CI 0.76–68.61]), the confidence intervals were very wide, indicating a small sample size.

Hospital admission for asthma and AD, and emergency room visits for asthma were significant predictors for death. Patients with concomitant AD and asthma have increased risk of hospital admission due to both AD and asthma. Increased focus on diagnosing and managing asthma in patients with AD is warranted. Early intensive patient education and written action plans, including early use of oral corticosteroids at home, are the key components to decrease emergency room visits and hospitalizations for asthma.²⁶

4.1 | Limitations

Subjects with AD and asthma in the present cohort comprised those seen in hospital and a number of private clinics. Adults treated by the general practitioner (GP) or private clinics not registered in the database with a diagnosis are not included in this cohort. Another important limitation is the lack of power to assess cause-specific mortality for subjects with concomitant AD and asthma concerning infectious, endocrine, gastrointestinal, neurologic, urogenital and psychiatric diseases. Finally, the registries did not have any data on important confounders such as BMI, smoking and alcohol consumption. In some analyses, the risk was reduced notably when adjusting the associations for age, sex, socio-economic status and educational level. Adjusting for BMI, smoking or alcohol in these cases may further attenuate the associations.

5 | CONCLUSION

The overall risk of death was increased in adults with hospital-diagnosed concomitant AD and asthma compared to adults with asthma only, and death due to pulmonary disease in adults with concomitant AD and asthma was increased compared to adults with AD only. Further, AD- and asthma-related hospitalization and emergency room visit for asthma was a predictor for death in adults with concomitant AD and asthma. Increased focus on development and implementation of early preventative and improved management

strategies for patients with concomitant AD and asthma to modify increased risk of mortality is warranted. Further, future studies should investigate whether asthma is more severe in patients with concomitant AD and asthma compared to asthma only.

CONFLICT OF INTEREST

ZA and SFT have no conflict of interest related to this paper. CSU has received personal fees for attending advisory boards, lectures, etc., from AstraZeneca, Sanofi Genzyme, GSK, Boehringer Ingelheim, Novartis, ALK-Abello, Mundipharma, TEVA, Actelion, Orion Pharma and Chiesi outside the submitted work. JPT has attended advisory boards for Eli Lilly, Regeneron, Pfizer, LEO Pharma, AbbVie and Sanofi Genzyme, received speaker honorarium from LEO Pharma, AbbVie, Regeneron and Sanofi Genzyme, and received research grants from Regeneron and Sanofi Genzyme. AE has received research funding from Pfizer, Eli Lilly, Novartis, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, UCB, Mylan, Bristol-Myers Squibb and Janssen Pharmaceuticals.

AUTHOR CONTRIBUTIONS

Z.A. conceived the presented idea. Z.A. carried out the analyses, wrote and revised the paper. A.E. verified the analytical methods. S.F.T., J.P.T., C.S.U. and A.E. supervised the study and contributed equally to supervision of the paper.

DATA AVAILABILITY STATEMENT

No raw data are available for sharing, due to national legislation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Atopic
dermatitis
n=8,095

Age and sex matches
(without Atopic
dermatitis)
n=32,380

Atopic
dermatitis
and asthma
n=1,201

Atopic
dermatitis
only
n=6,894

Neither atopic
dermatitis nor
asthma
n=31,502

asthma
only
N=878

Cohort Entry Date
(Diagnosis of atopic dermatitis)
Day 0

Covariate assessment window
(age, sex, socioeconomic status, education level)
Days [0,0]

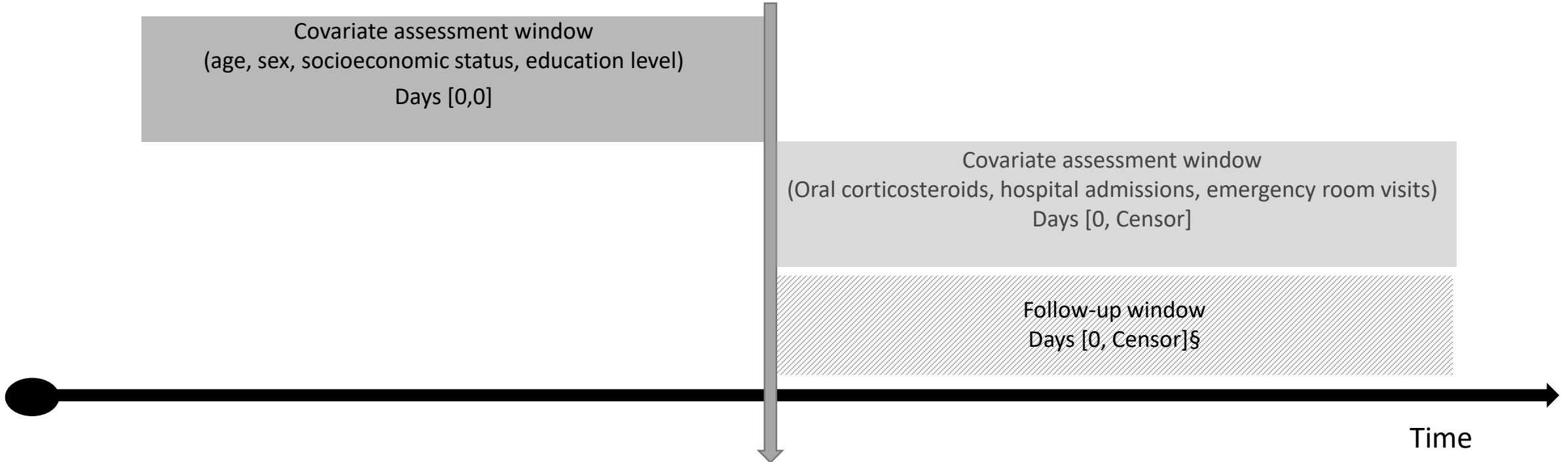
Covariate assessment window
(Oral corticosteroids, hospital admissions, emergency room visits)
Days [0, Censor]

Follow-up window
Days [0, Censor]§

1. Diagnosis of atopic
dermatitis

2. Diagnosis of atopic
dermatitis

Time



Supplementary material a

Supplementary Table 1: List of codes used in the study

Name	Code type	Code	Detailed description
Atopic dermatitis	ICD-10	L20	Atopic dermatitis
Asthma	ICD-10	J45	Asthma
	ICD-10	J46	Status asthmaticus
	ICD-9	493	Asthma
Asthma medication	ATC	R03AK	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics
	ATC	R03AL	Adrenergics in combination with anticholinergics incl. triple combinations with
	ATC	R03BA	Glucocorticoids
Systemic corticosteroids	ATC	H02AB02	<u>D</u> examethasone
	ATC	H02AB04	<u>M</u> ethylprednisolone
	ATC	H02AB06	<u>P</u> rednisolone
	ATC	H02AB07	<u>P</u> rednisone
	ATC	H02AB09	<u>H</u> ydrocortisone
Hospital admission for atopic dermatitis	ICD-10	L-20	Atopic dermatitis
Emergency room visit for asthma	ICD-10	J45	Asthma
	ICD-10	J46	Status asthmaticus
	ICD-9	493	Asthma
Hospital admission for asthma	ICD-10	J45	Asthma
	ICD-10	J46	Status asthmaticus
	ICD-9	493	Asthma
Cause of death	ICD-10	A00–B99	Certain infectious and parasitic diseases
	ICD-10	C00–D48	Neoplasms
	ICD-10	E00–E90	Endocrine, nutritional and metabolic diseases
	ICD-10	F01–F99	Mental, Behavioral and Neurodevelopmental disorders
	ICD-10	G00–G99	Diseases of the nervous system
	ICD-10	I00–I99	Diseases of the circulatory system

	ICD-10	J00–J99	Diseases of the respiratory system
	ICD-10	K00–K93	Diseases of the digestive system
	ICD-10	N00–N99	Diseases of the genitourinary system
	ICD-10	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
		H00-H59	Diseases of the eye and adnexa
		H60-H95	Diseases of the ear and mastoid process
L00-L99		Diseases of the skin and subcutaneous tissue	
	M00-M99	Diseases of the musculoskeletal system and connective tissue	
Educational level	The Danish National Patient Registry	H10	Primary school
	The Danish National Patient Registry	H20 H30 H35	High school education Vocational education Eligible training courses
	The Danish National Patient Registry	H40 H50 H60	Short higher education Medium higher education Bachelor Degrees
	The Danish National Patient Registry	H70 H80	Long higher education Ph.d. and research educations

* The Danish Health Care Classification System (SKS)

Supplementary Table 2: Characteristics of participants with atopic dermatitis and background population.

Characteristic	Atopic dermatitis	Background population
Number	8,095	32,380
Sex, n (%)		
Men	3,092 (38.2)	12,368 (38.2)
Women	5,003 (61.8)	20,012 (61.8)
Age at death, years		
Mean SD	69.36 (14.73)	73.26 (15.07)
Socioeconomic status, n(%)		
Lowest	1,626 (20.1)	6,469 (19.9)
Below average	1,645 (20.3)	6,450 (19.9)
Average	1,611 (19.9)	6,484 (20.0)
Above average	1,549 (19.1)	6,546 (20.2)
Highest	1,664 (20.6)	6,431 (19.8)
Education level, n (%)		
Primary school	1,505 (18.6)	6,737 (20.8)
High/vocational school	3,399 (42.0)	14,018 (43.3)
Short and medium	2,148 (26.5)	7,931 (24.5)
Higher	976 (12.1)	3,335 (10.3)
Systemic corticosteroids n (%)		
Mean (SD)	3,118 (38.5)	2,967 (9.16)
	7.51 (15.66)	4.79 (10.63)

Abbreviations: SD, standard deviation

Supplementary Table 3: Complete dataset analysis for mortality among subjects with concomitant atopic dermatitis and asthma, atopic dermatitis only, asthma only, and neither atopic dermatitis nor asthma, by cause of death

Cause of Death	Atopic dermatitis and asthma	Atopic dermatitis only	Asthma only	Neither atopic dermatitis nor asthma
All-cause mortality Events (n) IR (95% CI)	93 10.27 (8.39-12.58)	330 7.09 (6.37-7.90)	53 7.49 (5.73-9.81)	954 4.33 (4.06-4.61)
Pulmonary disease Events (n) IR (95% CI)	19 2.09 (1.33-3.28)	41 0.88 (0.65-1.14)	20 2.83 (1.83-4.39)	99 0.44 (0.36-0.54)
Cardiovascular disease Events (n) IR (95% CI)	21 2.31 (1.51-3.56)	73 1.57 (1.25-1.97)	7 0.99 (0.47-2.08)	235 1.06 (0.93-1.21)
Neoplasm/cancer Events (n) IR (95% CI)	30 3.31 (2.32-4.74)	100 2.15 (1.76-2.61)	19 2.67 (1.71-4.21)	358 1.63 (1.46-1.80)
Infectious disease Events (n) IR (95% CI)	<3 0.22 (0.05-0.88)	9 0.19 (0.10-0.37)	<3 0.14 (0.02-1.00)	18 0.08 (0.05-0.13)
Endocrine disease Events (n) IR (95% CI)	<3 0.22 (0.06-0.88)	14 0.30 (0.18-0.51)	<3 0.28 (0.07-1.13)	38 0.17 (0.13-0.24)
Gastrointestinal disease Events (n) IR (95% CI)	7 0.77 (0.37-1.62)	32 0.69 (0.49-0.97)	<3 0.14 (0.02-1.00)	46 0.21 (0.16-0.28)
Neurologic disease Events (n) IR (95% CI)	<3 0.22 (0.06-0.88)	15 0.32 (0.19-0.53)	-	30 0.14 (0.09-0.19)
Urogenital disease Events (n) IR (95% CI)	<3 0.11 (0.02-0.78)	<3 0.04 (0.01-0.17)	<3 0.14 (0.02-1.00)	13 0.06 (0.03-0.10)
Psychiatric disease Events (n) IR (95% CI)	6 0.66 (0.29-1.47)	19 0.41 (0.26-0.64)	<3 0.14 (0.02-1.00)	61 0.28 (0.22-0.36)
Other diseases Events (n) IR (95% CI)	<3 0.22 (0.06-0.88)	3 0.06 (0.02-0.22)	-	17 0.07 (0.05-0.12)

Abbreviations: IR, incidence rates per 1,000 person-years; CI, confidence interval
Data on one or two individuals are shown as <3, due to data security requirements.

Supplementary table 4: Complete dataset analysis for the risk for cause-specific mortality

Cause of Death	Atopic Dermatitis only vs neither atopic dermatitis nor asthma	Asthma only vs neither atopic dermatitis nor asthma	Atopic dermatitis and asthma vs atopic dermatitis only	Atopic dermatitis and asthma vs asthma only	Atopic dermatitis and asthma vs neither atopic dermatitis nor asthma
All-cause mortality HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	1.54 (1.36-1.75) p<0.001 1.92 (1.69-2.19) p<0.001	1.72 (1.30-1.26) p<0.001 1.45 (1.09-1.91) p=0.009	1.55 (1.23-1.96) p<0.001 1.85 (1.51-2.27) p<0.001	1.36 (0.97-1.90) p=0.072 1.52 (1.07-2.15) p=0.019	2.36 (1.90-2.92) p<0.001 2.27 (1.83-2.62) p<0.001
Pulmonary disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	1.88 (1.30-2.73) P=0.001 2.55 (1.75-3.72) p<0.001	6.20 (3.83-10.03) p<0.001 5.62 (3.46-9.11) p<0.001	2.51 (1.45-4.35) p<0.001 2.32 (1.35-3.99) P=0.002	0.73 (0.39-1.38) p=0.341 0.86 (0.44-1.66) p=0.661	4.65 (2.85-7.61) p<0.001 5.02 (3.04-8.29) p<0.001
Cardiovascular disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	1.32 (1.01-1.73) p=0.049 1.70 (1.29-2.24) p<0.001	0.92 (0.43-1.96) p=0.839 0.78 (0.37-1.67) p=0.528	1.67 (1.03-2.74) p=0.039 1.14 (0.69-1.87) p=0.599	2.30 (0.98-5.43) p=0.055 2.87 (1.19-6.94) p=0.019	2.16 (1.38-3.38) p<0.001 2.07 (1.32-3.24) p=0.001
Neoplasm/cancer HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	1.31 (1.04-1.63) P=0.019 1.52(1.21-1.90) p<0.001	1.64 (1.04-2.61) p=0.034 1.36 (0.86-2.17) p=0.187	1.57 (1.04-2.37) p=0.030 1.15 (0.76-1.74) p=0.482	1.23 (0.69-2.18) p=0.476 1.21 (0.67-2.17) p=0.511	2.03 (1.39-2.94) p<0.001 1.85 (1.27-2.69) p=0.001
Infectious disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	2.12 (0.92-4.88) p=0.076 2.51 (1.07-5.66) p=0.033	1.71 (0.23-12.86) p=0.599 1.41 (0.18-10.61) p=0.744	1.32 (0.27-6.21) p=0.727 0.97 (0.20-4.67) p=0.972	1.55 (0.14-17.18) p=0.718 1.92 (0.16-23.11) p=0.606	2.69 (0.62-11.63) p=0.183 2.76 (0.62-12.16) p=0.178
Endocrine disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	1.74 (0.94-3.21) p=0.076 2.25 (1.21-4.16) p=0.010	1.66 (0.40-6.90) p=0.482 1.41 (0.34-5.87) p=0.634	0.75 (0.17-3.53) p=0.714 0.53 (0.12-2.39) p=0.415	0.77 (0.11-5.50) p=0.800 1.12 (0.13-9.03) p=0.915	1.28 (0.31-5.33) p=0.728 1.15 (0.27-4.83) p=0.840
Gastrointestinal disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	3.22 (2.04-5.07) p<0.001 4.09 (2.58-6.40) p<0.001	0.67 (0.09-4.84) p=0.690 0.57 (0.08-4.12) p=0.575	1.16 (0.51-2.65) p=0.714 0.71 (0.31-1.63) p=0.422	5.45 (0.67-44.31) p=0.113 6.11 (0.74-50.71) p=0.094	3.67 (1.65-8.12) p=0.001 3.30 (1.47-7.37) p=0.004
Neurologic disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	2.40 (1.29-4.47) p=0.006 3.14 (1.68-5.87) p<0.001		0.65 (0.14-2.84) p=0.568 0.43 (0.09-1.95) p=0.681		1.58 (0.37-6.63) p=0.527 1.42 (0.33-6.09) p=0.630
Urogenital disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	0.73 (0.16-3.24) p=0.681 0.90 (0.20-4.06) p=0.899	2.44 (0.31-18.64) p=0.391 1.85 (0.23-14.34) p=0.557	2.60 (0.23-28.74) p=0.435 3.41 (0.16-73.04) p=0.652	0.76 (0.05-12.17) p=0.847 2.80 (0.12-63.46) p=0.516	1.91 (0.24-14.60) p=0.533 1.87 (0.24-14.60) p=0.547
Psychiatric disease HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	1.25 (0.72-2.17) p=0.417 1.64 (0.94-2.86) p=0.079	0.49 (0.07-3.57) p=0.487 0.44 (0.06-3.17) p=0.412	2.06 (0.78-5.13) p=0.146 1.33 (0.51-3.45) p=0.554	4.66 (0.56-38.72) p=0.154 6.88 (0.58-80.94) p=0.125	2.35 (1.01-5.45) p=0.045 2.54 (1.08-2.96) p=0.031
Other diseases HR (95% CI) p-value HR _{adjusted} (95% CI) p-value	0.84 (0.24-2.87) P=0.784 1.06 (0.30-3.63) P=0.926		3.59 (0.60-21.55) p=0.161 3.20 (0.51-19.88) p=0.121		2.84 (0.65-12.30) p=0.162 2.63 (0.60-11.51) p=0.197

Abbreviations: HR, Hazard ratio; CI, confidence interval; Adjusted for sex, age, socioeconomic status, and educational level

Supplementary Table 5: complete dataset analysis for predictors of all-cause mortality

Atopic dermatitis and asthma				
	Events (n)	IR (95% CI)	HR (95% CI), p-value	HR_{adjusted} (95% CI), p-value
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	7	3.47 (1.65-7.28)		
Systemic corticosteroid 1-5	29	7.28 (5.06-10.47)	2.08 (0.91-4.76), p=0.081	1.19 (0.51-2.75), p=0.678
Systemic corticosteroid >5	57	18.64 (14.37-24.16)	5.29 (2.41-11.61), p<0.001	1.84 (0.82-4.09), p=0.137
Hospital admissions for atopic dermatitis				
Hospital admission 0	74	9.63 (7.66-12.09)		
Hospital admission = 1	19	13.84 (8.29-21.70)	1.50 (0.91-2.48), p=0.115	1.43 (0.85-2.42), p=0.172
Emergency room visits and hospital admissions for asthma				
Emergency room visit 0	65	8.62 (6.76-11.00)		
Emergency room visit ≥1	28	18.39 (12.69-26.63)	2.08 (1.33-3.24), p=0.001	1.69 (1.06-2.67), p=0.025
Hospital admission 0	21	4.40 (2.87-6.75)		
Hospital admission 1-3	38	11.32 (8.29-15.56)	2.58 (1.51-4.39), p<0.001	1.81 (1.04-3.12), p=0.036
Hospital admission >3	34	36.48 (26.06-51.05)	8.22 (4.77-14.17), p<0.001	3.03 (1.71-5.38), p<0.001
Atopic dermatitis only				
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	85	3.66 (2.96-4.52)		
Systemic corticosteroid 1-5	123	7.32 (6.13-8.73)	2.06 (1.52-2.64), p<0.001	1.49 (1.13-1.98), p=0.004
Systemic corticosteroid >5	101	16.31 (13.42-19.82)	4.46 (3.34-5.95), p<0.001	1.87 (1.39-2.51), p<0.001
Hospital admissions for atopic dermatitis				
Hospital admission 0	238	5.76 (5.07-6.54)		
Hospital admission = 1	71	14.51 (11.50-18.31)	2.60 (1.99-3.39), p<0.001	1.77 (1.35-2.31), p<0.001
Asthma only				
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	10	3.39 (1.82-6.31)		
Systemic corticosteroid 1-5	20	7.03 (4.54-10.91)	2.05 (0.96-4.39), p=0.063	1.64 (0.75-3.59), p=0.213
Systemic corticosteroid >5	23	17.91 (11.91-26.96)	5.17 (2.46-10.87), p<0.001	1.68 (0.77-3.66), p=0.184
Emergency room visits and hospital admissions for asthma				
Emergency room visit 0	44	7.27 (5.41-9.76)		
Emergency room visit ≥1	9	8.86 (4.60-17.02)	1.23 (0.60-2.52), p=0.568	1.53 (0.71-3.33), p=0.279
Hospital admission 0	10	2.47 (1.33-4.59)		
Hospital admission 1-3	36	12.93 (9.33-27.93)	5.16 (2.56-10.41), p<0.001	2.44 (1.15-5.18), p=0.019
Hospital admission >3	7	28.85 (13.75-60.51)	11.58 (4.41-30.45), p<0.001	3.98 (1.38-11.53), p=0.011
Not atopic dermatitis nor asthma				
Systemic corticosteroid prescriptions regardless of duration and indication				
Systemic corticosteroid 0	566	3.12 (2.87-3.38)		
Systemic corticosteroid 1-5	271	8.41 (7.46-9.46)	2.68 (2.32-3.10), p<0.001	1.68 (1.45-1.94), p<0.001
Systemic corticosteroid >5	117	18.16 (15.15-21.77)	5.79 (4.75-7.07), p<0.001	1.71 (1.39-2.09), p<0.001

Abbreviations: IR, incidence rate per 1,000 person-years; HR, hazard ratio; CI, confidence interval

Adjusted for sex, age, socioeconomic status, and educational level

Supplementary Figure 1: Flow diagram of study population

Supplementary Figure 2: Illustration of study flow