Atopic dermatitis and risk of atrial fibrillation or flutter: a 35-year follow-up study

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Capsule summary:

- We found a 20% increased risk of atrial fibrillation in patients with hospital-diagnosed (moderate-to-severe) atopic dermatitis. This finding may be mediated through persistent systemic inflammation.
- Although the absolute risk is low, the typical early onset of atopic dermatitis provides an opportunity for promoting a heart healthy lifestyle in these patients.

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Conflicts of interest: None

Ethical approval: The study was approved by the Danish Data Protection Agency (record no. 2013-41-2237; 2016-051-000001). Danish legislation does not require approval by an ethical review board or informed consent from patients for registry-based studies. The Danish Patient Safety Authority approved access to medical records for the validation of diagnoses (record no. 3-3013-1526/1/). The study protocol is available from the corresponding author upon request.

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Abbreviations:
CI: Confidence interval
COPD: chronic obstructive pulmonary disease
DNPR: Danish National Patient Registry
ICD: International Classification of Diseases

ABSTRACT

Background: Atopic dermatitis is characterized by chronic inflammation, which is a risk factor for atrial fibrillation.

Objective: To examine the association between hospital-diagnosed atopic dermatitis and atrial fibrillation.

Methods: Using linked population-based Danish registries, we identified persons with an in- or out-patient hospital diagnosis of atopic dermatitis during 1977–2013 and an individually-matched comparison cohort. We followed cohorts until death, emigration, atrial fibrillation diagnosis or until 2013. We compared 35-year risk of atrial fibrillation and estimated hazard ratios with 95% confidence intervals (CIs) using Cox regression, adjusting for birth year and sex. We validated 100 atopic dermatitis diagnoses from a dermatological department through medical record review.

Results: We included 13,126 persons with atopic dermatitis and 124,211 comparators followed for a median of 19.3 years. The 35-year risk of atrial fibrillation was 0.81% and 0.67%, respectively. The positive predictive value of atopic dermatitis diagnoses was 99%. The hazard ratio was 1.2 (95% CI: 1.0–1.6) and remained increased after adjusting for various atrial fibrillation risk factors.

Limitations: Limited to moderate-to-severe atopic dermatitis and no lifestyle data.

Conclusions: Patients with hospital-diagnosed atopic dermatitis have a 20% increased long-term risk of atrial fibrillation, but the absolute risk remains low.

Capsule summary:

- We found a 20% increased risk of atrial fibrillation in patients with hospital-diagnosed (moderate-to-severe) atopic dermatitis. This finding may be mediated through persistent systemic inflammation.
- Although the absolute risk is low, the typical early onset of atopic dermatitis provides an opportunity for promoting a heart healthy lifestyle in these patients.

INTRODUCTION

Atopic dermatitis is a pruritic chronic inflammatory skin disorder.[1] Prevalence has increased up to three-fold over the last three decades and it now affects 10–20% of children in industrialized countries,[1] qualifying it as the most common chronic childhood disease. However, the common concept that atopic dermatitis is limited to childhood is being abolished. Adult-onset atopic dermatitis is more frequent than previously appreciated and childhood atopic dermatitis often persist until adulthood or may relapse after long periods with inactive disease.[1] Thus, up to 10% of adults suffer from atopic dermatitis.[1]

Atrial fibrillation is the most commonly sustained rhythm disorder with a prevalence of 4% in persons aged 60 years or older.[2] It is associated with severe morbidity and mortality from *e.g.* stroke.[2] Inflammation is a recognized risk factor for atrial fibrillation, as supported by an increased occurrence in patients with rheumatoid arthritis and elevated levels of inflammatory biomarkers.[3-5] Atopic dermatitis may thus predispose to atrial fibrillation due to persistent low-grade systemic inflammation and/or increased prevalence of atrial fibrillation risk factors, *e.g.*, obesity, hypertension and diabetes.[2,6-10]

To add evidence on this sparsely examined hypothesis,[9] we conducted a nationwide population-based 35-year cohort study to examine whether patients with hospital-diagnosed (moderate-to-severe) atopic dermatitis are at long-term increased risk of atrial fibrillation.

METHODS

Study population

We used the Danish National Patient Registry (DNPR) to identify individuals born in Denmark between 1 January 1947 and 1 January 1983 (approximately 2.7 million) who

received a first-time hospital diagnosis of atopic dermatitis from 1 January 1977 until 1 January 2013.[11] At each hospital discharge or outpatient visit, one primary diagnosis and optional secondary diagnoses are recorded by the physician in charge using the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter. We considered all inpatient, outpatient and emergency room diagnoses of atopic dermatitis, using the date of admission or start of outpatient follow-up as the 'index date'. Table 1 shows definitions for study variables.

We used the Civil Registration System[12] to sample a comparison cohort including 10 individuals from the general population matched to each atopic dermatitis patient by sex and birth year. We assigned persons in the comparison cohort with the same index date as their corresponding atopic dermatitis patient.

Validation

We examined the validity of 100 randomly selected inpatient and outpatient diagnoses of atopic dermatitis from the Department of Dermatology, Aarhus University Hospital during 1977 to 2016. One author (JLR) scrutinized patients' medical records, using as reference standard the diagnosis stated by the treating physician in the medical record.

Atrial fibrillation or flutter

We used the DNPR to obtain information on all inpatient or outpatient primary or secondary diagnoses of atrial fibrillation in the study population. Because of overlapping pathophysiology, we included both atrial fibrillation and flutter.[13,14] To ensure that only incident diagnoses were considered, we excluded persons in the study cohorts who had atrial fibrillation recorded before index date.

Patient characteristics

We considered patients to have 'severe atopic dermatitis' if they filled a prescription for azathioprine, cyclosporine, mycophenolate, or methotrexate, which are used in systemic atopic dermatitis treatment,[1] or if they were admitted with atopic dermatitis coded as the primary reason for admission. We identified systemic treatments through the Danish National Prescription Registry, which was established in 1995 and includes records of all prescription drugs dispensed at Danish pharmacies, classified according to the Anatomical Therapeutic Chemical Classification.[15] As we were limited to patients diagnosed in the hospital-based setting, we considered patients to have at least moderate severity at outset. We included severity as a time-updated variable, *i.e.*, patients contributed person-time in the moderate category switching to the severe category for the remainder of the follow-up if and when they fulfilled the definition for severe atopic dermatitis. As an alternative measure of severity and activity, we used number of atopic dermatitis contacts (1, 2–4, 5–7, 8 or more). In this analysis, the index date was the first, second, fifth and eighth contact, respectively, for atopic dermatitis patients and their matched comparators. We also included diagnoses of allergic asthma or rhinitis as a measure of atopic multimorbidity.

We used the DNPR to identify the following potential atrial fibrillation risk factors:[2,4,8] chronic obstructive pulmonary disease (COPD), cardiovascular disease (ischemic heart disease, heart failure, hypertension, and structural valve problems), rheumatic disease, sleep apnea, hospital-diagnosed obesity, hyperthyroidism, chronic kidney disease, diabetes, and alcohol-related disease. We used the DNPR[11] and Danish National Prescription Registry[15] to identify procedures and treatment as disease proxies to increase completeness when relevant (*e.g.*, antidiabetic drugs as a proxy for diabetes). We included these conditions as they could be more prevalent among atopic dermatitis patients because of immune-dysregulation, shared pathophysiology, adverse effects of treatment, or affected lifestyle choices,[1,6,7,9] thereby explaining an association

with atrial fibrillation. In the main analysis, we considered the covariables as potential confounders, including records available before index date. In additional analyses, we added the possibility that they could be mediators by time-updating variables with information recorded after start of follow-up. Thus, a person was considered to have a given disease from the first registry record defining that disease and onwards.

We used education registries from Statistics Denmark[16] to identify the highest educational level on the index date, classified as short-term (7–10 years), medium-term (11–12 years), or long-term (13+ year) education.

Statistical analysis

For the validation sample, we computed the positive predictive value with 95% confidence intervals (based on Wilson's score method[17]) as the proportion of confirmed diagnoses.

We followed cohorts from the index date until atrial fibrillation diagnosis, emigration, death, or 1 January 2013, whichever occurred first. We produced descriptive statistics for the cohorts. We plotted the cumulative incidence of atrial fibrillation for atopic dermatitis and comparison cohorts, with death as a competing risk. We used Cox proportional-hazards regression stratified on matched set to compute hazard ratios (HRs) with 95% confidence intervals, as a measure of the relative risk of the association between atopic dermatitis and atrial fibrillation or flutter. We used time from index date as the underlying time scale. To explore the role of certain variables as mediators, we fitted several regression models of increasing complexity. Model 1 was unadjusted, accounting only for matched factors. Model 2 adjusted additionally for baseline atrial fibrillation risk factors. Model 3 adjusted also for educational level for those with non-missing information for this variable (*i.e.*, a complete case analysis).

In stratified analyses, we examined whether the association varied by sex and presence of allergic asthma or rhinitis. We also examined results for subgroups defined by age at first atopic dermatitis contact (0–19, 20–39, 40+ years), severity, and number of atopic dermatitis hospital contacts. We performed severity analyses with delayed entry until 1 January 1996 to ensure at least 1 year of prescription history.[15]

We performed three sensitivity analyses. We repeated model 2 with atrial fibrillation risk factors included as time-updated covariates (mediation analysis). We repeated the main analyses with delayed entry until 1 January 1996 in all comparisons. We repeated severity analyses adding phototherapy as another criterion for severe atopic dermatitis.

We verified the assumption of proportional hazards by visual inspection of plots of the log(-log(survival)) *vs.* log(survival time). Analyses were performed with Stata® 14.2 (StataCorp LP, Texas, US).

RESULTS

We were able to retrieve all but one medical records for the validation sample. Medical review confirmed 98/99 diagnoses, yielding a positive predictive value of 99% (95% CI: 95%–100%).

We identified 13,144 eligible persons with atopic dermatitis and 124,487 matched comparators, subsequently excluding 18 atopic dermatitis patients (together with 165 comparators) and 111 comparators with prevalent atrial fibrillation. Distribution of characteristics was quite similar among atopic dermatitis patients and comparators (Table 2). Males accounted for 43%. Median age was 19 years (interquartile range: 6–29). Allergic asthma or rhinitis and COPD were more common in atopic dermatitis patients.

Median follow-up was 19.3 years (total 2,787,675 person-years). The cumulative incidence proportion of atrial fibrillation after 35 years of follow-up was 0.81% in the atopic dermatitis cohort and 0.67% in the comparison cohort (Figure 1). The corresponding unadjusted HR was 1.2 (95% CI: 1.0–1.6) for atopic dermatitis patients *vs.* the matched comparison cohort (Table 3). Increasing level of adjustment had no substantial effect on estimates (HRs 1.2 [95% CI: 0.9–1.5]).

We found some evidence of variation by sex (HR 1.6 for females vs. 1.0 for males), diagnosis age (HR 1.6 for 0–19 years vs. 1.0–1.1 for older age groups), coexisting diagnosis of allergic asthma/rhinitis (HR 1.7 for presence vs 1.0 for absence of diagnosis), and number of atopic dermatitis contacts for exposed (HR 4.0 for >8 contacts vs. 1.0 for <2 contacts) (Table 3). The HR was 1.1 (95% CI: 0.8–1.6) for moderate and 1.3 (95% CI: 0.9–1.8) for severe atopic dermatitis. These potential differences were also apparent on the absolute scale comparing unadjusted rates (Table 3).

Estimates were attenuated, but remained increased, in the mediation analysis incorporating time-update for covariables (Table 4). There were no substantial changes in estimates when analyzing with delayed entry or when using phototherapy as a proxy for severe atopic dermatitis in addition to other systematic therapies and admissions (Table 4).

DISCUSSION

This long-term follow-up study shows evidence that hospital-diagnosed atopic dermatitis is associated with a 20% increased relative risk of atrial fibrillation. Characteristics associated with particular high risk estimates were female sex, young age at first hospital diagnosis, and indicators for severe disease (atopic multimorbidity, frequent hospital contact).

To our knowledge, only one previous epidemiologic study has examined this topic.[9] In a population-based UK cohort study adult persons with versus without atopic dermatitis had an HR for atrial fibrillation of 1.11 (99% confidence interval [CI]: 1.04 to 1.18), increasing to 1.17 (99% CI 1.08–1.27) for moderate and 1.38 (99% CI: 1.17 to 1.62) for severe disease.[9] There was no evidence that age, sex or asthma modified the association. Although their study was limited adults and had a median follow-up of only 5.1 years, our results are in accordance with findings for moderate-to-severe disease. Similarly, adjustment for potential mediators of the association, explained findings only partly.

A potential mechanisms underlying the observed association is systemic inflammation, similar to that presumed to link psoriasis and rheumatic disorders to atrial fibrillation.[3-5,18] Arrhythmogenic effects of atopic dermatitis treatments is also possible, although evidence for such adverse effects is limited.[19-22] The more pronounced association for those with many hospital contacts and coexisting atopic conditions supports these mechanisms. Study size precluded analyses of the impact of individual systemic drugs for atopic dermatitis. Psychosocial factors and unhealthy lifestyle resulting from atopic dermatitis, *e.g.*, stress, elevated blood pressure, smoking, diabetes, and hypercholesterolemia, could play a role as well,[6,7] although obesity is not more prevalent in European patients with atopic dermatitis.[10] The slight attenuation from adjustment for various atrial fibrillation risk factors could support this hypothesis.

The population-based design in a universal healthcare system with virtually complete follow-up of patients eliminates selection bias in our study.[12] Furthermore, follow-up was longer than the UK study (median 19.3 vs. 5.1 years).[9] Nevertheless, the highest possible attained age was between 30 and 65 years, which is relatively low considering the usual age of onset of atrial fibrillation.[23] Furthermore, some patients may have had atopic dermatitis before entering our study. Because of such onset

misclassification, atrial fibrillation risk factors recorded at baseline may be intermediate steps (rather than confounders) linking atopic dermatitis to atrial fibrillation.

The validity of atopic dermatitis diagnoses was found high in our validation sample at a single dermatology department. Although the positive predictive value may be unrepresentative of other departments, misclassification of atopic dermatitis in the entire study population is unlikely to depend on the outcome (atrial fibrillation) as data were prospectively collected. Such non-differential misclassification tends to produce underestimates and can therefore not explain an observed association. Furthermore, although some patients may actually have had other cutaneous conditions associated with atrial fibrillation (*e.g.*, venous insufficiency or pruritus in chronic kidney disease), these conditions are rare in young persons, who in our study predominated (50% were <20 years at index diagnosis) and had the HR of atrial fibrillation associated with atopic dermatitis.

Limited variation by severity may result from misclassification, as we lacked clinical information on severity or activity. Furthermore, we defined severe disease by systemic treatments, which could oppose the proposed mechanism by decreasing inflammation and thus lead to underestimates for the severe category in our study. Finally, as most patients with atopic dermatitis are diagnosed outside the hospital setting, our study already represents the most severe end of the disease spectrum. This incompleteness may have affected the possibility to detect variation by severity and potential generalizability to mild atopic dermatitis.

The positive predictive value of atrial fibrillation diagnoses in the DNPR is high (92–99%).[24-27] We did not distinguish between atrial fibrillation patterns (paroxysmal, persistent, or permanent) or between atrial fibrillation and flutter. As atrial fibrillation accounts for >90% of patients registered with these codes,[26] our results are likely driven by this arrhythmia. Still, as atrial fibrillation and flutter share risk factors and to some

degree pathophysiology,[13,14] we expect the results to apply to both. Regarding completeness, most patients with atrial fibrillation are diagnosed during a hospital admission or at a hospital outpatient clinic according to Danish guidelines,[28] and very few cardiologists work outside the public hospital system in Denmark. However, because of regular follow-up of patients with severe atopic dermatitis, opportunity for atrial fibrillation diagnosis may be greater than for matched comparators (*i.e.*, ascertainment bias).

We adjusted for education and several comorbidities, but cannot exclude misclassification of these mediators, residual confounding, and confounding from unmeasured variables.

Finally, statistical uncertainty (as measured by width of the confidence intervals) should be considered.[29] Although our data are best compatible with a 20% increase in the rate of atrial fibrillation among atopic dermatitis patients, our data are reasonably compatible with a small (10%) decrease to a substantially elevated (50%) increase in relative risk. Importantly, subgroup analyses should be interpreted cautiously as the lower number of events reduce the statistical precision.

In conclusion, patients with hospital-diagnosed (moderate-to-severe) atopic dermatitis have a 20% increased long-term risk of atrial fibrillation compared with the general population. Although the clinical implications are limited by a low absolute risk of atrial fibrillation, the typical early onset of atopic dermatitis may provide clinicians with a unique opportunity for promoting a heart healthy lifestyle to reduce risk for cardiovascular disease, including atrial fibrillation.

Contributions: MS and MO conceived the study idea and designed the study. MO and JLR established and designed the cohort. SAJS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data

analysis. All authors participated in the discussion and interpretation of the results. SAJS organized the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version.

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Figure 1. Risk of atrial fibrillation or flutter in patients with hospital-diagnosed atopic dermatitis and a matched comparison cohort, adjusted for birth year and sex, Denmark, 1977–2013

Table 1. Registry codes used to identify study variables[1]

Variable	Code(s)
Atopic dermatitis	*ICD-8*: 691; *ICD-10*: L20;
Azathioprine	*ATC code*: L04AX01; *Procedure code*: BWHB83
Methotrexate	*ATC code*: L01BA01, L04AX03; *Procedure code*: BWHA115
Cyclosporine	*ATC code*: L04AD01; *Procedure code*: BOHJ20
Mycophenolate	*ATC code*: L04AA06; *Procedure code*: BOHJ22
Phototherapy	*Procedure code*: BNGA1, BNGA2, BNGA3, BNGA4
Atrial fibrillation and flutter	*ICD-8*: 42793, 42794; *ICD-10*: I48;
Allergic asthma	*ICD-8*: 493; *ICD-10*: J450;
Allergic rhinitis	*ICD-8*: 50709; *ICD-10*: J301–J304;
Chronic obstructive pulmonary disease or non-allergic asthma.	*ICD-8*: 491, 492; *ICD-10*: J41, J42, J43, J44, J45 (except J450), J46; *ATC code*: R03 (at least two prescriptions) except if the person has a prevalent allergic asthma diagnosis
Cardiovascular disease, including structural valve problems, hypertension, ischemic heart disease, and heart failure	*ICD-8*: 393-398, 400-404, 410-414, 425, 42709, 42710, 42711, 42719, 78249; *ICD-10*: I05-I09, I10-I15, I20-I25, I34-I37, I390, I393, I42 (excl. I426 included below), I43, I50, I511A, Q22; *ATC code*: C01DA, C02, C03, C07, C08, C09, B01AC04, B01AC06, N02BA01; *Procedure code*: 30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30109, 30119, 30120, 30129, 30139, 30149, 30159, 30169, 30179, 30189, 30199, 30200 30300, 30310, 30320, 30330, 30340, 30350, 30360, 30600, 30620, 30640, 30660, 30700, 30701, 30709, 30719, 30720, 30729, 30740, 30780, 30799, 30800, 30810, 30910, 30920, 30925, 30939, 30959, 30990, 31100, 31101, 31119, 31129, 31130, 31180, 31199, 31200, 31210, 31220, 31229, 31230, 31249, 31259, 31268, 31269, 31280, 31299, 31310, 30350, 30354, 30240, KFNA-E, KFNH20, KFM (excluding KFMA32, KFMD10-14, KFMH10), KFK (excluding KFKA32, KFKC70, KFKH10), KFG (excluding KFGA32) KFJE (excluding KFJE42), KFJF, KFJW, KFNG, KFNF
Rheumatic disease	*ICD-8*: 28709, 69609, 712, 716, 734, 446; *ICD-10*: D690B, G737, G058A, H221B, I328A, I328B, I398C, I398E, I418A, I528A, I776, L931, L932, L95, M05-M07, M30–M36, M45, M793, N085, N164;
Sleep apnea	*ICD-10*: G473
Obesity	*ICD-8*: 277; *ICD-10*: E65-E66;

Hyperthyroidism	*ICD-8*: 242; *ICD-10*: E05, H062, E060, E062; *ATC code*: H03B
Chronic kidney disease	*ICD-8*: 584, 792, 9977, Y9509; *ICD-10*: L298C, G638A, E853B, T825A, T825B, T825C, T856C, I120, I131, I132, I770, N165, N180, N183, N184, N185, N188, N189, N19, T824, T861, Z49, Z94, Z992, T817E1; *Procedure code*: KJAK10, KJAK11, KJAK13, KJAK14, KTJA30, KTJA32, KTJA35, KKAS, BJFD2, BJFZ, BJKB, BUFC1, BWDC5, ZZ0151A, ZZ4341, ZZ4342, ZZ4343, ZZ4346, ZZ4347, ZZ4348, ZZ4350, 57480, 57490, 87409, 87419, 87420, 87430, 87431, 87432, 87440, 92390, 92400, 94300, 94340
Diabetes mellitus	*ICD-8*: 249-250; *ICD-10*: E10-E14, H360, O24 (except O244), H360, N083, DG632; *ATC code*: A10
Alcoholism-related disorder or prescription	*ICD-8*: 291, 303, 57109-57110, 57710, 979, 980; *ICD-10*: F10, G312, G621, G721, I426, K292, K700, K703, K860, R780, T510, T519, Z721; *ATC code*: N07BB01

ICD: International Classification of Diseases; ATC: Anatomical Therapeutic Chemical
[1]Only primary and secondary diagnoses are included from the Danish National Patient Registry

Table 2. Characteristics at cohort entry for persons with hospital-diagnosed atopic dermatitis compared with a matched comparison cohort, Denmark, 1977–2013

	Atopic dermatitis		Matched comparators	
	No.	**%**	**No.**	**%**
Total	13126	100	124211	100
Sex				
Male	5630	43	54024	43
Female	7496	57	70187	57
Birth year				
1947–1956	1266	10	11800	9
1957–1966	2631	20	24525	20
1967–1982	9229	70	87886	71
Age at start of follow-up				
0–19	6509	50	64274	52
20–39	5208	40	47165	38
40–63	1409	11	12772	10
Allergic asthma or rhinitis	842	6	1002	1
Sleep apnea	6	0	54	0
Hospital-diagnosed obesity	88	1	835	1
Rheumatic disease	110	1	498	0
Chronic kidney disease	35	0	87	0
COPD	1536	12	5648	5
Cardiovascular disease	459	3	3149	3
Diabetes mellitus	84	1	771	1
Hyperthyroidism	32	0	325	0
Alcohol-related disease	243	2	1681	1
Educational level				
Short term education	2608	20	23380	19
Medium term education	5172	39	53272	43
Long term education	5109	39	45512	37
Missing	237	2	2047	2

All variables in the table are measured at start of follow-up

Table 3. Observations, events, person-years, rates and hazard ratios of atrial fibrillation or flutter for persons with hospital-diagnosed atopic dermatitis compared with a matched comparison cohort, Denmark, 1977-2013

	Observations	Events	Person-years	Rate (per 100000)	Model 1 (unadjusted)[1]	Model 2 (+atrial fibrillation risk factors)[2]	Model 3 (+educational level)[3]
Overall							
Comparators	124211	631	2530240	24.9	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	13126	80	257435	31.1	1.2 (1.0–1.6)	1.2 (0.9–1.5)	1.2 (0.9–1.5)
Sex							
Males							
Comparators	54024	402	1188398	33.8	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	5630	43	119291	36.0	1.0 (0.7–1.4)	1.0 (0.7–1.3)	1.0 (0.7–1.4)
Females							
Comparators	70187	229	1341842	17.1	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	7496	37	138143	26.8	1.6 (1.1–2.3)	1.6 (1.1–2.3)	1.6 (1.1–2.3)
Age at start of follow-up							
0–19 years							
Comparators	64274	190	1716596	11.1	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	6509	29	170203	17.0	1.6 (1.1–2.4)	1.6 (1.1–2.4)	1.6 (1.1–2.4)
20–39 years							
Comparators	47165	253	698660	36.2	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	5208	28	74928	37.4	1.0 (0.7–1.6)	1.0 (0.7–1.5)	1.0 (0.7–1.5)
40–63 years							
Comparators	12772	188	114984	163.5	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	1409	23	12304	186.9	1.1 (0.7–1.8)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
Severity							

Moderate							
Comparators	76169	300	911576	32.9	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	8357	38	98463	38.6	1.2 (0.8–1.7)	1.1 (0.8–1.6)	1.1 (0.8–1.6)
Severe							
Comparators	45873	280	637486	43.9	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	5023	39	69348	56.2	1.3 (0.9–1.8)	1.2 (0.9–1.8)	1.3 (0.9–1.8)
Allergic asthma/rhinitis							
No							
Comparators	94260	435	1669224	26.1	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	9979	47	170487	27.6	1.0 (0.8–1.4)	1.0 (0.7–1.4)	1.0 (0.7–1.4)
Yes							
Comparators	41472	196	861016	22.8	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	4347	33	86948	38.0	1.7 (1.2–2.5)	1.6 (1.1–2.4)	1.7 (1.1–2.4)
Number of atopic dermatitis contacts							
1 contact							
Comparators	124211	417	1787221	23.3	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	13126	45	182210	24.7	1.0 (0.8–1.4)	1.0 (0.8–1.4)	1.0 (0.8–1.4)
2–4 contacts							
Comparators	40452	162	619928	26.1	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	4277	27	62925	42.9	1.6 (1.1–2.5)	1.6 (1.0–2.4)	1.6 (1.0–2.4)
5–7 contacts							
Comparators	7653	37	79909	46.3	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	806	3	7964	37.7	0.7 (0.2–2.4)	0.8 (0.3–2.8)	0.9 (0.3–2.8)
8+ contacts							
Comparators	3052	15	43182	34.7	1 (reference)	1 (reference)	1 (reference)
Atopic dermatitis	327	5	4336	115.3	3.2 (1.1–8.8)	3.9 (1.3–12.0)	4.0 (1.3–12.6)

[1]Stratified by matched set to account for matching factors (birth year, sex, index date).
[2]Additionally adjusted for baseline chronic obstructive pulmonary disease, cardiovascular disease, rheumatic disease, sleep apnea, hospital-diagnosed obesity, hyperthyroidism, chronic kidney disease, diabetes mellitus, and alcohol-related disease.
[3]Additionally adjusted for educational level (complete-case analysis).

Table 4. Hazard ratios (95% CIs)[1] of atrial fibrillation or flutter for persons with hospital-diagnosed atopic dermatitis compared with a matched comparison cohort, Denmark, 1977–2013. Sensitivity analyses.

	Sensitivity analysis 1[2]	**Sensitivity analysis 2[3]**			**Sensitivity analysis 3[4]**		
	Model 2	**Model 1**	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
Overall	1.0 (0.8–1.3)	1.2 (1.0–1.6)	1.2 (0.9–1.5)	1.2 (0.9–1.5)	NA	NA	NA
Sex							
Male	0.9 (0.6–1.2)	1.0 (0.7–1.4)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	NA	NA	NA
Female	1.5 (1.0–2.1)	1.6 (1.1–2.3)	1.6 (1.1–2.3)	1.6 (1.1–2.3)	NA	NA	NA
Diagnosis age							
0–19	1.5 (1.0–2.4)	1.5 (1.0–2.3)	1.5 (1.0–2.3)	1.5 (1.0–2.3)	NA	NA	NA
20–39	0.9 (0.6–1.3)	1.1 (0.7–1.6)	1.0 (0.7–1.5)	1.0 (0.7–1.6)	NA	NA	NA
40–63	0.9 (0.6–1.5)	1.1 (0.7–1.8)	1.1 (0.7–1.7)	1.1 (0.7–1.7)	NA	NA	NA
Severity							
Moderate	1.1 (0.7–1.5)	1.2 (0.8–1.7)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	1.2 (0.9–1.7)	1.2 (0.8–1.7)	1.2 (0.8–1.7)
Severe	1.1 (0.7–1.5)	1.3 (0.9–1.8)	1.2 (0.9–1.8)	1.3 (0.9–1.8)	1.2 (0.9–1.7)	1.2 (0.9–1.7)	1.2 (0.9–1.7)
Allergic asthma/rhinitis							
No	0.9 (0.7–1.2)	1.0 (0.8–1.4)	1.0 (0.7–1.4)	1.0 (0.7–1.4)	NA	NA	NA
Yes	1.4 (0.9–2.2)	1.7 (1.1–2.4)	1.6 (1.1–2.4)	1.6 (1.1–2.4)	NA	NA	NA
Number atopic dermatitis of contacts							
<2 contacts	0.9 (0.7–1.3)	1.1 (0.8–1.5)	1.0 (0.8–1.4)	1.1 (0.8–1.4)	NA	NA	NA
2–4 contacts	1.3 (0.8–2.0)	1.6 (1.1–2.5)	1.5 (1.0–2.4)	1.5 (1.0–2.4)	NA	NA	NA
5–7 contacts	1.1 (0.3–4.4)	0.5 (0.1–2.1)	0.6 (0.1–2.4)	0.6 (0.1–2.5)	NA	NA	NA
8+ contacts	2.9 (0.6–14.1)	3.2 (1.1–8.8)	3.9 (1.3–12.0)	4.0 (1.3–12.6)	NA	NA	NA

[1]Based on a Cox regression model stratified by matched set to account for matching factors (birth year, sex, index date). Model 1 was unadjusted. Model 2 additionally adjusted for chronic obstructive pulmonary disease, cardiovascular disease, rheumatic disease, sleep apnea,

hospital-diagnosed obesity, hyperthyroidism, chronic kidney disease, diabetes mellitus, and alcohol-related disease. Model 3 additionally adjusted for educational level (complete-case analysis).
[2]Repeated model 2 with atrial fibrillation risk factors included as time-updated covariates (mediation analysis)
[3]Repeated the main analyses with delayed entry until 1 January 1996 in all comparisons
[4]Repeated severity analyses adding phototherapy as another criterion for severe atopic dermatitis.