

Letter to the Editor

Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis

To the Editor:

Atopic dermatitis (AD) is a chronic inflammatory skin condition with a particularly high prevalence in countries with a Western lifestyle.¹ AD can have a substantial negative effect on a patient's quality of life and is associated with a higher risk of depression, increased consumption of tobacco and alcohol, and a sedentary lifestyle.^{2,3}

Recently, there has been a growing interest in the putative cardiovascular comorbidities of dermatologic diseases. In patients with psoriasis, an increased prevalence of cardiovascular risk factors but possibly also proinflammatory mediators appears to contribute to an increased cardiovascular risk.⁴ However, studies investigating links between cardiovascular disease and AD are few in number, although recent studies have found positive associations between AD and cardiovascular risk factors, ischemic stroke, and myocardial infarction (MI).^{3,5,6} Importantly, it remains unclear whether the inflammatory nature of AD or the increased burden of AD-associated cardiovascular risk factors are primary determinants of the apparent increased risk. Therefore, this population-based study examined the effect of AD on the risk of adverse cardiovascular outcomes among Danish adults, taking selected lifestyle factors into account.

In brief, health care is free in Denmark, and we used the Danish nationwide registers to obtain information on vital statistics, morbidity, medication use, cause of death, and tax-reported income. As cases, the study cohort comprised all Danish citizens aged 15 years or older with a hospital diagnosis of AD starting from January 1, 1997, and followed until December 31, 2011; migration; death; or the occurrence of an end point. Each case was matched (age, sex, and calendar time) with 5 control subjects. Patients with MI or ischemic stroke before study start were excluded.

Patients were classified as having severe AD when they received systemic therapy for AD (azathioprine, methotrexate, cyclosporine, and/or mycophenolate mofetil). AD without such therapy was classified as mild. The primary end points were a diagnosis of MI, ischemic stroke, and cardiovascular death, respectively, and the secondary end point was major adverse cardiovascular events (MACEs; ie, a composite of the primary end points). Incidence rate ratios (IRRs) were estimated by using Poisson regression. For further details, see the [Methods](#) section in this article's Online Repository at www.jacionline.org.

A total of 5,762,813 Danish citizens aged 15 years or older were identified (1997–2012) and served as the source population. The final study population comprised a total of 26,898 mild and 2,527 severe cases of AD, respectively, and 145,372 control subjects without an AD diagnosis. The study flow chart is available in [Fig E1](#) in this article's Online Repository at www.jacionline.org. Baseline prevalence of comorbidities, smoking, and use of pharmacotherapy was higher in patients with severe AD compared with the reference population and patients with mild AD, respectively ([Table I](#)). The mean age of occurrence of MI was 62.2 (SD, 15.7), 61.7 (SD, 15.0), and 58.7 (SD, 12.7)

TABLE I. Population characteristics at study's start

	Reference population (n = 145,372)	Mild AD (n = 26,898)	Severe AD (n = 2,527)
Age (y), mean (SD)	24.5 (13.4)	23.8 (12.9)	34.8 (16.5)
Age (y), median (range)	18.7 (84.6)	17.8 (81.4)	34.8 (84.6)
Women (%)	78,338 (53.9)	14,514 (54.0)	1,336 (52.9)
Men (%)	67,034 (46.1)	12,384 (46.0)	1,191 (47.1)
Socioeconomic status, mean (SD)	2.0 (1.4)	1.9 (1.4)	2.9 (1.2)
Smoking ever (%)	6,085 (4.2)	1,563 (5.8)	342 (13.5)
Comorbidities (%)			
Alcohol abuse	1,261 (0.9)	327 (1.2)	37 (1.5)
Cardiac dysrhythmias	284 (0.2)	80 (0.3)	16 (0.6)
Diabetes	1,024 (0.7)	198 (0.7)	32 (1.3)
Hypertension	1,745 (1.2)	332 (1.2)	92 (3.6)
Inflammatory bowel disease	236 (0.2)	67 (0.3)	56 (2.4)
Medication (%)			
Antidepressants	2,446 (1.7)	574 (2.1)	124 (4.9)
Antiplatelet drugs	882 (0.6)	183 (0.7)	54 (2.1)
Cholesterol-decreasing drugs	859 (0.6)	156 (0.6)	64 (2.5)
Loop diuretics	575 (0.4)	180 (0.7)	52 (2.1)

Baseline characteristics regarding age, sex, socioeconomic status, comorbidities, and medication use in the reference population, mild AD group, and severe AD group, respectively, are shown.

years in control subjects, patients with mild AD, and patients with severe AD, respectively. The mean age of stroke was 58.3 (SD, 8.8), 60.6 (SD, 19.4), and 62.8 (SD, 15.9) years in the 3 respective groups, and finally, the mean age of cardiovascular death was 61.6 (SD, 18.2), 63.1 (SD, 19.0), and 63.1 (SD, 15.8) years, respectively. Incidence rates are presented in [Table E1](#) in this article's Online Repository at www.jacionline.org. Notably, age- and sex-adjusted IRRs for MI, ischemic stroke, cardiovascular death, and MACEs were reduced in patients with mild AD. The results remained consistent after additional adjustment for socioeconomic status, smoking, medication, and comorbidities. For patients with severe AD who received systemic therapy, the age- and sex-adjusted IRRs yielded significantly increased risk estimates of ischemic stroke, cardiovascular death, and MACEs, whereas the estimate for MI was not significant. In the fully adjusted models IRRs were nonsignificant across all end points ([Table II](#)).

Our study suggests that lifestyle factors associated with severe AD are likely to explain the apparent increased risk of cardiovascular disease found in previous studies.^{3,5,6} For example, a US population-based study recently showed that patients with AD not only smoked more and consumed more alcohol than control subjects but also had a higher body mass index, more hypertension and prediabetes, and a decreased level of physical activity, respectively.³ A Taiwanese study found an increased risk of ischemic stroke in patients with AD, whereas another study found a higher risk of coronary artery disease, angina, MI, congestive heart failure, ischemic stroke, and peripheral vascular disease in patients with AD.^{5,6} Also, subclinical coronary artery disease with increased coronary artery calcium scores was found in

TABLE II. IRRs of outcomes in patients with AD

	Age and sex adjusted			Fully adjusted*		
	IRR	95% CI	P value	IRR	95% CI	P value
MI						
Mild AD	0.82	0.66-1.02	.070	0.73	0.59-0.91	<.05
Severe AD	1.39	0.95-2.03	.091	1.06	0.72-1.56	.761
Stroke						
Mild AD	0.92	0.78-1.11	.381	0.82	0.68-0.98	<.05
Severe AD	1.51	1.08-2.10	<.05	1.19	0.85-1.65	.317
Cardiovascular death						
Mild AD	0.97	0.82-1.15	.732	0.71	0.60-0.84	<.001
Severe AD	1.46	1.07-2.02	<.05	1.06	0.77-1.46	.723
Composite end point						
Mild AD	0.92	0.82-1.04	.196	0.80	0.70-0.90	<.001
Severe AD	1.53	1.23-1.91	<.001	1.17	0.94-1.46	.159

Multivariate analyses with Poisson regression models were used to estimate IRRs. IRR estimates were adjusted for age and sex because patients in the severe AD group were older.

*IRR estimates further adjusted for socioeconomic status, smoking, comorbidities, and medication use.

Danish patients with severe and long-term AD without known cardiovascular disease.⁷ Collectively, patients with severe AD appear to have increased risk of cardiovascular disease, but this risk difference is likely explained by an increased burden of cardiovascular risk factors rather than by the inflammatory nature of AD.

Additionally, after adjustment for potential confounding factors, we found a significantly decreased risk of cardiovascular adverse events in patients with mild AD. Affluent patients are more resourceful and presumably more compliant with health care recommendations and prescribed treatment regimens, resulting in better AD disease control, and it is tempting to speculate that such patients as a group might not progress from mild to severe AD to the same extent as nonresourceful patients. However, it is possible that our adjustments for socioeconomic status did not fully compensate for such mechanisms and that these could have contributed to the apparent decreased risk of cardiovascular disease in patients with mild AD. Interestingly, a former Japanese study found a lower prevalence of hypertension in patients with AD when compared with healthy subjects.⁸

The high accuracy of the Danish registries, as well as the available information on socioeconomic status, medication, and comorbidities, allows for large-scale nationwide analyses in which selection and recall bias are minimized. However, we only included patients treated at hospitals, and misclassification of patients with mild and severe AD could have occurred. Hospital diagnoses of AD were made by physicians, but these specific International Classification of Disease (ICD) codes have not been validated. Furthermore, the systemic treatments that are used in patients with AD are also prescribed for other inflammatory diseases. Also, AD severity could have been defined otherwise, such as by the number of hospital consultations. A wide variety of comorbid conditions and social factors, including body

mass index, sedentary lifestyle, and lipid levels, were not available, although we attempted to adjust for such risk factors by using surrogate markers (socioeconomic status, comorbidities, and medication use).

In conclusion, we found an overall higher incidence of adverse cardiovascular outcomes in patients with presumed severe AD, but this was explained by an increased burden of comorbidities and detrimental lifestyle behavior. Increased focus on AD-associated comorbidities and early intervention aimed at modifiable risk factors for cardiovascular disease are warranted, especially in patients with severe AD.

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METHODS

The study was approved by the Danish Data Protection agency (reference 2007-58-0015, int. ref. GEH-2014-018, I-suite 02736), and register studies do not require approval from an ethics committee in Denmark. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations.^{E1}

The Danish National Health Service provides all Danish citizens tax-supported health care, which guarantees free access to general practitioners and hospitals. Citizens are assigned a unique personal identification number at birth or immigration, which allows for linkage among the nationwide Danish administrative and health registers.^{E2} Data on morbidity were obtained from the Danish National Patient Register, which contains information on all hospital admissions, procedures, and outpatient visits. ICD-8 codes were used from 1978 to 1994, and ICD-10 codes were used from 1994 to present; hospital procedures (including hospital-based pharmacological treatment) were coded as treatment procedure (SKS) codes.^{E3} Information on dispensed drugs was obtained from the Danish Registry of Medicinal Products Statistics, where all prescription-based drugs are recorded. Drugs are coded by the international Anatomical Therapeutic Chemical (ATC) classification.^{E4} Information on tax-reported household income is recorded by Statistics Denmark.^{E5} Data on deaths and causes of death were obtained through ICD-10 codes from the National Causes of Death Registry.^{E6} Data from the abovementioned registers are encrypted and rendered anonymous when used for research purposes.

Study population

The study cohort comprised the entire Danish population aged 15 years or older starting from January 1, 1997, and followed until December 31, 2011; migration; death; or the occurrence of an end point. Subjects with a history of MI or ischemic stroke before study's start, as well as subject's with missing information on migration, were excluded to enable evaluation of the temporal relationship between exposure and outcome and ensure accurate risk-time allocation. Patients were identified and included by their first inpatient or outpatient hospital diagnosis of AD (ICD-8 691 and ICD-10 L20) from the Danish National Patient Register. Because a substantial proportion of AD diagnoses are made before the age of 15 years, patients with prevalent AD were included in the study at the latter of either January 1, 1997, or their 15th birthday, respectively. Cardiac dysrhythmias and inflammatory bowel disease were detected based on hospital diagnoses. Alcohol abuse was defined by diagnoses of alcohol abuse or conditions strongly related to alcohol abuse (eg, alcoholic liver disease), pharmacologic treatment with drugs used in alcohol dependence, and treatment interventions for alcohol dependence. Hypertension and smoking were defined by using previously developed algorithms.^{E7,E8} Diabetes was defined by either a hospital diagnosis or use of glucose-decreasing drugs. Comorbidities were identified as binary variables at baseline and during the follow-up period and were included in the final adjusted model. We calculated an index of socioeconomic status between 0 and 4 based on the average gross annual income (standardized by age) during a 5-year period before study inclusion. Subjects were matched with a ratio of 1:5 between cases and control subjects by using risk-set sampling. Control subjects were matched with cases by sex, age, and calendar period and randomly sampled from all noncases in the Danish population. The index date for control subjects was the index date of the corresponding case.

Disease severity

Patients were stratified based on presumed severity of AD. Patients were considered to have severe disease when they received systemic

immunosuppressive therapy against AD (ie, azathioprine [ATC code L04AA06 or SKS code BWHB83], methotrexate [ATC code L01BA01, L04AX03 or SKS code BWHB115], cyclosporine [ATC code L04AD01 or SKS code BOHJ20], or mycophenolate mofetil [ATC code L04AA06 or SKS code BOHJ22]). Patients with an AD diagnosis who did not receive systemic therapy during the study period were classified as having mild AD.

End points

The primary end points were a diagnosis of MI (I21-I22), ischemic stroke (I63-I64), and cardiovascular death (I00-I99), respectively, and the secondary end point was MACEs (ie, a composite of MI, ischemic stroke, and cardiovascular death). The identification of MI and ischemic stroke has previously been validated in the National Patient Register.^{E9,E10} End points were investigated in separate nonexclusive analyses (ie, occurrence of an end point in one analysis did not result in censoring in the other analyses).

Statistical analysis

Categorical variables were presented as frequencies with percentages, and continuous variables were presented as means with SDs. Incidence rates were presented per 10,000 person-years at risk. Crude and adjusted (adjusted for age, sex, socio-economic status, smoking, comorbidity, and medication) IRRs were calculated by using Poisson regression models. Wald χ^2 tests were used to test differences between parameter estimates derived from Poisson regression analyses. Results were presented with 95% CIs, where applicable, and *P* values of less than .05 were considered statistically significant. Statistical analyses were performed with STATA software (version 11.0; StataCorp, College Station, Tex) and SAS statistical software (version 9.2; SAS Institute, Cary, NC).

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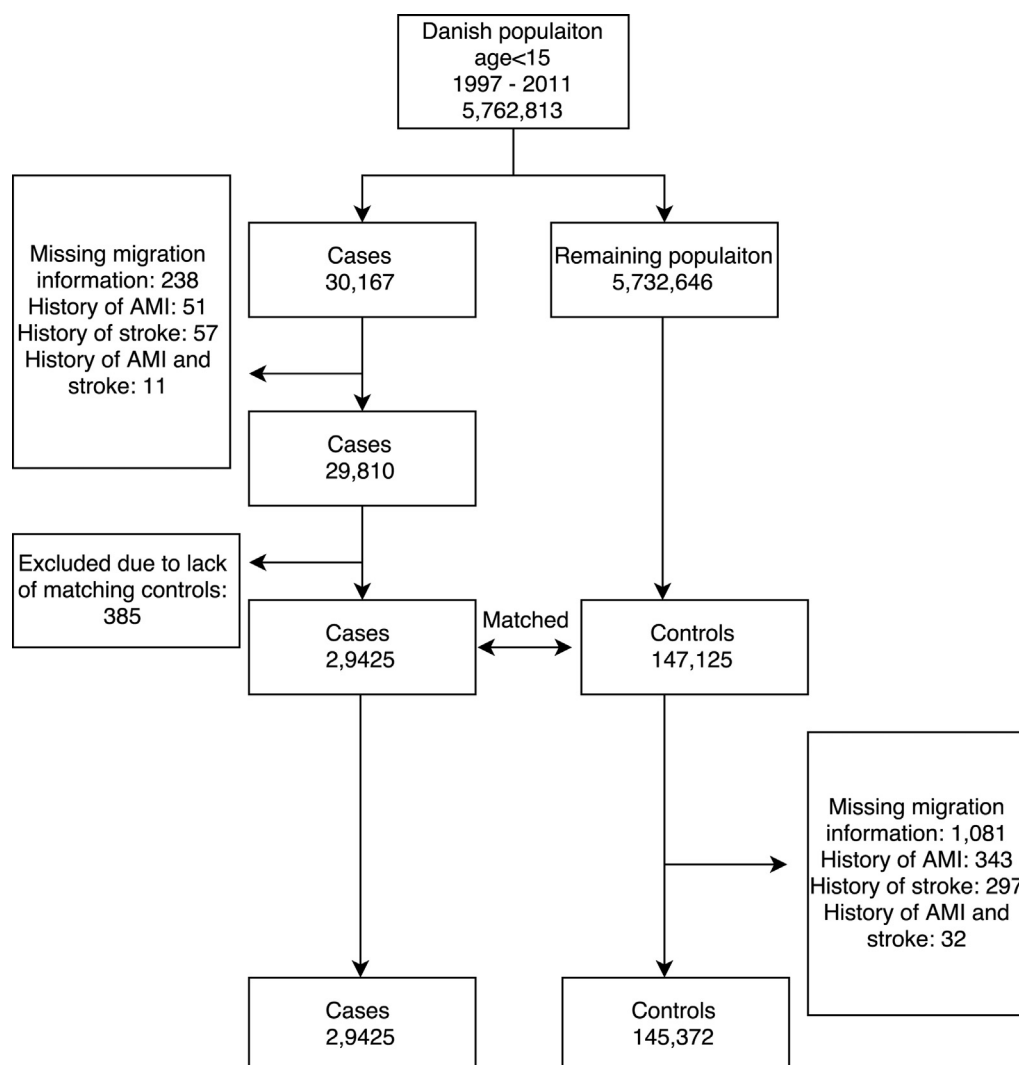


FIG E1. All Danish subjects aged 15 years or older between January 1, 1997, and December 31, 2011, served as the source population. All subjects with a hospital diagnosis of AD were identified as cases and matched with healthy control subjects at a ratio of 1:5 on age, sex, and calendar time.

TABLE E1. Incidence rates of outcomes per 10,000 person-years in the reference population and patients with AD, respectively

	Reference population	Patients with mild AD	Patients with severe AD
MI			
No. of events	612	97	28
Person-years	1,288,156.3	211,977.8	13,784.2
Incidence rate	4.75	4.58	20.3
95% CI	4.39-5.14	3.75-5.58	14.02-29.42
Stroke			
No. of events	868	147	37
Person-years	1,287,169.4	211,436.8	13,713.7
Incidence rate	6.74	6.95	26.98
95% CI	6.31-7.21	5.91-8.17	19.55-37.24
Cardiovascular death			
No. of events	723	163	41
Person-years	1,290,179.5	212,679.0	13,967.6
Incidence rate	5.60	7.66	29.35
95% CI	5.21-6.03	6.57-8.94	21.61-39.87
Composite end point			
No. of events	1,839	316	85
Person-years	1,285,192.4	210,807.7	13,548.9
Incidence rate	14.31	14.99	62.74
95% CI	13.67-14.98	13.43-16.74	50.72-77.60

Total number of MIs, strokes, cardiovascular deaths, and MACEs during the study period and incidence rates were calculated per 10,000 person-years in the reference population, mild AD group, and severe AD group, respectively.