

ORIGINAL ARTICLE

Atopic dermatitis and risk of ischemic stroke: A nationwide population-based study

Vincent Yi-Fong Su^{1,8}, Tzeng-Ji Chen^{2,3,8}, Chiu-Mei Yeh², Kun-Ta Chou^{1,8,11}, Man-Hsin Hung³, Szu-Ying Chu^{4,6,8,11}, Kang-Cheng Su^{1,8}, Yu-Sheng Chang^{7,8}, Ya-Hsuan Lin⁹ & Chia-Jen Liu^{3,5,8,10}

¹Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ²Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ³Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ⁴Department of Dermatology, Taipei Veterans General Hospital, Taipei, Taiwan, ⁵Department of Internal Medicine, National Yang-Ming University Hospital, Yilan, Taiwan, ⁶Department of Dermatology, National Yang-Ming University Hospital, Yilan, Taiwan, ⁷Division of Allergy, Immunology & Rheumatology, and Department of Medicine, Taipei Medical University Shuang Ho Hospital, New Taipei City, Taiwan, ⁸School of Medicine, National Yang-Ming University, Taipei, Taiwan, ⁹College of Medicine, Chang Gung University, Taoyuan, Taiwan, ¹⁰Institute of Public Health, National Yang-Ming University, Taipei, Taiwan, and ¹¹Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan

Background. Epidemiological studies have shown a strong association between systemic inflammatory diseases, particularly allergic diseases, and cardiovascular diseases. However, the relationship between atopic dermatitis (AD) and ischemic stroke remains unclear.

Method. The study identified 20,323 AD patients and 20,323 comorbidity-matched subjects between 2005 and 2008. The two cohorts were followed until 31 December 2009. Ischemic stroke and other cardiovascular events were determined.

Results. During the follow-up period, 301 (1.48%) patients in the AD cohort and 228 (1.12%) matched subjects experienced ischemic stroke. After multivariate adjustment, patients with AD had a 1.33-fold (95% confidence interval (CI), 1.12–1.59; $P=0.001$) increased incidence of ischemic stroke. Adjusted hazard ratios for the risk of ischemic stroke in patients with mild, moderate, and severe AD were 1.20 (95% CI, 1.00–1.45; $P=0.052$), 1.64 (95% CI, 1.23–2.19; $P=0.001$), and 1.71 (95% CI, 1.15–2.56; $P=0.008$), respectively. The log-rank test showed a higher cumulative incidence of ischemic stroke in the severe AD group than in the moderate and mild AD groups during the follow-up period ($P<0.001$).

Conclusions. AD may be an independent risk factor for ischemic stroke, and risk of ischemic stroke increases with AD severity.

Key words: Atopic dermatitis, cardiovascular disease, ischemic stroke

Introduction

Stroke is a medical emergency that usually causes neurological damage, sequelae, and mortality. It is the leading cause of adult disability and death worldwide (1). The most common cause of

Key messages

- This large population-based study demonstrated that patients with AD had an increased risk of ischemic stroke.
- We also demonstrated an 'exposure-response relationship', in that the patients with severe AD had a higher risk of ischemic stroke than did those with less severe forms of the condition.

ischemic stroke is thrombosis, arterial embolism, or atherosclerosis (2). Risk factors for stroke include old age, hypertension, previous stroke or transient ischemic attack, diabetes, hypercholesterolemia, and atrial fibrillation. Epidemiological studies have shown a strong association between systemic inflammatory diseases, particularly allergic diseases, and cardiovascular disease.

Atopic dermatitis (AD) is a chronic inflammatory condition associated with hypersensitivity to environmental allergens. The incidence of AD has increased dramatically in the past 30–40 years (3), and AD has become a major skin disease in developing and developed countries (4,5). Recent research has suggested that AD is an allergic disease in which systemic inflammation involves more than just the skin. However, the relationship between AD and ischemic stroke remains unclear. Case-control studies reported enhanced platelet activation and reduced fibrinolysis in patients with AD (6,7,8), but no large-scale study has addressed this issue. The aim of this study was to determine the risk of ischemic stroke in patients with AD using a nationwide database.

Materials and methods

Database

Taiwan's National Health Insurance (NHI) program, initiated by the government in 1995, provides comprehensive health care to almost all Taiwanese citizens, with a coverage rate of more than 99% of Taiwan's entire population (9). The National Health Research Institute (NHRI) of Taiwan manages and publicly releases for research purposes multiple NHI databases that include information about basic patient characteristics; detailed claims data for examinations, disease management, and drug prescriptions; and diagnoses for all admitted patients and outpatients. The NHRI created a research database including a random sample of 1,000,000 subjects from the registry of all NHI enrollees in 2000, with the encryption of personal information that could identify any individual patient. We obtained data sets from this nationally representative cohort from the NHRI for use as our research database. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No. 201205043AC).

Study design and population

In this retrospective cohort study utilizing a nationwide database, we enrolled patients aged 20 or older with newly diagnosed AD (code 691.X in the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM)) between 1 January 2005 and 31 December 2008. Subjects who have a past history of stroke before the enrollment date were excluded from the study group.

Comparison group

Subjects without AD were randomly selected from the same data set. Each patient with newly diagnosed AD in the NHRI database was pair-matched with one subject of the same age and sex and with partially the same comorbidities and using the same diagnosis index date. Vascular protection medications and five comorbidities (lung cancer, chronic obstructive pulmonary disease, allergic rhinitis, asthma, and psoriasis) were not matched. We selected comparison subjects using incidence density sampling by computer programming (10). In the comparison group, subjects who have past history of stroke before enrollment were excluded as the study group.

Outcome measures

The primary outcome of interest was ischemic stroke (ICD-9 code 436, 433.x, 434.x, 437.1x) after the initial diagnosis of AD. All ischemic stroke diagnoses included in the analysis were accompanied by computed tomographic or magnetic resonance images taken within 14 days during hospitalization. We did not include suspected clinical diagnoses lacking confirmatory imaging. Because patients with the diagnosis of stroke could be exempted from co-payment under the NHI program, the diagnosis of stroke must be made by physicians. To clarify whether AD affects the other cardiovascular diseases, the alternative end-point of the study was the occurrence of acute myocardial infarction (AMI) or heart failure (HF) during the follow-up period. To determine total cardiovascular events including ischemic stroke and AMI and HF, competing risk survival analyses adjusting for age, sex, comorbidities, and medications were carried out with modified Cox's proportional hazards model. All enrollees were followed from the date of enrollment until the first diagnosis of ischemic stroke, AMI, HF, or censored date of death, withdrawal from the insurance, or until 31 December 2009.

Potential confounders

In the analysis of the effect of AD on the outcome of ischemic stroke, we controlled for age and sex and identified the following comorbidities as potential confounders: diabetes mellitus (ICD-9 code 250), atrial fibrillation (ICD-9 code 427.31), hypertension (ICD-9 codes 401.0, 401.1, 401.9, 402–405, 437.2), coronary artery disease (ICD-9 codes 410, 411), valvular heart disease (ICD-9 codes 394–396, 424), peripheral artery occlusive disease (ICD-9 code 444.2), chronic kidney disease (ICD-9 codes 580–587), and dyslipidemia (ICD-9 codes 270.0–270.2, 272.4). To adjust the severity of cardiovascular risk, subjects prescribed with the following vascular protection medications were seen as potential confounders: statins (Anatomic Therapeutic Chemical, World Health Organization (ATC) codes: C10AA, C10BA, C10BX); angiotensin-converting enzyme inhibitor (ATC codes: C09A, C09B)/angiotensin II receptor-blockers (ATC codes: C09C, C09D); aspirin (ATC code: N02BA01)/clopidogrel (ATC code: B01AC04), and warfarin (ATC code: B01AA03). To adjust the possible surveillance bias, we use dermatologist visits as a variable in the statistical analyses.

Severity of AD

We also performed a subgroup analysis after stratifying patients with AD based on medication using the defined daily dose (DDD), considered to be the average daily adult maintenance dose of a drug recommended for a given indication. The World Health Organization (http://www.whocc.no/atc_ddd_index/) has recommended the use of the DDD to measure the amount of a prescribed drug. We used the DDDs of oral antihistamines and corticosteroids used to treat AD to compare medication regimens among patients in the study cohort according to the same standard with the following formula: number of DDDs = total amount of drug / amount of drug in a DDD. Patients prescribed < 28 DDDs of oral antihistamines and corticosteroids in the past year were classified as non-users of AD medication (mild AD group). Patients prescribed ≥ 28 DDDs of oral antihistamines and < 28 DDDs of oral corticosteroids were assigned to the moderate AD group, and those prescribed ≥ 28 DDDs of oral corticosteroids were assigned to the severe AD group.

Statistical analyses

Data extraction and computation were performed using the Perl programming language (version 5.12.2). The Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, WA, USA) was used for data linkage, processing, and sampling. Statistical analysis was performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation or *n* (%) unless otherwise stated. Comparisons between groups were performed using Student's *t* test for continuous variables and Pearson's chi-square or Fisher's exact test, as appropriate, for categorical variables. The difference between cumulative incidence curves was tested with the log-rank test. The Cox's proportional hazards model was used to estimate the hazards ratio for the progression of outcome. Cox's proportional hazards models were used to test the association of AD with ischemic stroke, AMI, and HF. Cox's proportional hazards model in the competing risk analysis was performed by the STATA v.12 software (StataCorp LP, College Station, TX, USA). In the multivariable Cox's proportional hazard models, we used the forward selection method with likelihood ratio to build the best-fitting model for the variables. Risk factors with *P* values < 0.1 in the univariate model were entered into the

multivariable analysis. A P value < 0.05 was considered statistically significant.

Results

Clinical characteristics of the study population

We identified 28,612 patients newly diagnosed with AD between 1 January 2005 and 31 December 2008. After excluding patients aged < 20 years ($n = 6,782$) or with antecedent stroke ($n = 1,507$), 20,323 patients with AD were included in the analyses. Another 20,323 patients without AD were selected by 1:1 matching by age, sex, and comorbidities. The study subjects were predominantly female ($n = 12,583$, 61.9%), and the median age was 40 years (interquartile range, 29–54 years). Table I shows that basic characteristics and selected comorbidities were similar between groups.

Predictors of ischemic stroke risk and other cardiovascular events

During the follow-up period, 301 (1.48%) patients with AD and 228 (1.12%) comparison subjects experienced an ischemic stroke. The log-rank test showed a higher cumulative incidence of ischemic stroke in the AD group than in the matched cohort during the follow-up period ($P = 0.003$; Figure 1), suggesting that patients with AD had an increased risk of ischemic stroke in the long term. Compared with subjects without AD, stratified Cox's proportional hazard regression demonstrated that the crude hazard ratio (HR) for future ischemic stroke among patients with AD was 1.29 (95% confidence interval (CI), 1.09–1.54; $P = 0.003$). After adjusting for patients' age, sex, comorbidities, and medications, this HR was 1.33 (95% CI,

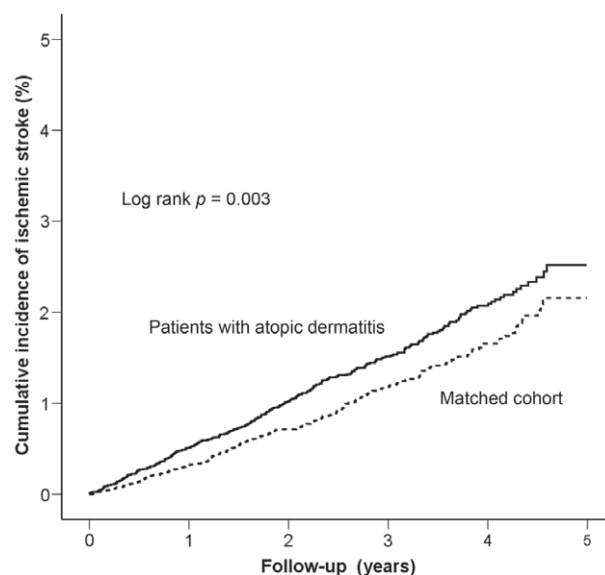


Figure 1. Cumulative incidence of ischemic stroke in patients with atopic dermatitis (AD) and matched cohort.

1.12–1.59; $P = 0.001$), suggesting that AD is an independent risk factor for ischemic stroke (Table II).

We identified the following independent factors determining the risk of future ischemic stroke: male sex (HR, 1.49; 95% CI, 1.25–1.78; $P < 0.001$), age (HR, 1.07; 95% CI, 1.06–1.08; $P < 0.001$), diabetes mellitus (HR, 1.34; 95% CI, 1.10–1.62; $P = 0.003$), hypertension (HR, 2.07; 95% CI, 1.63–2.63; $P < 0.001$),

Table I. Baseline characteristics of patients with atopic dermatitis (AD) and matched cohort.

Characteristics	Patients with AD ($n = 20,323$)		Matched cohort ($n = 20,323$)		P
	n	%	n	%	
Age, y, median (interquartile range)	40 (29–54)		40 (29–54)		
< 40	9,897	48.7	9,897	48.7	
≥ 40	10,426	51.3	10,426	51.3	
Female	12,583	61.9	12,583	61.9	
Male	7,740	38.1	7,740	38.1	
Diabetes mellitus	2,936	14.4	2,936	14.4	
Atrial fibrillation	151	0.7	151	0.7	
Hypertension	4,678	23.0	4,678	23.0	
Coronary artery disease	209	1.0	209	1.0	
Valvular heart disease	1,090	5.4	1,090	5.4	
PAOD	54	0.3	54	0.3	
Chronic kidney disease	1,657	8.2	1,657	8.2	
Dyslipidemia	4,459	21.9	4,459	21.9	
Lung cancer	97	0.5	88	0.4	0.556
COPD	3,570	17.6	3,044	15.0	< 0.001
Allergic rhinitis	7,078	34.8	5,647	27.8	< 0.001
Asthma	2,852	14.0	2,304	11.3	< 0.001
Psoriasis	345	1.7	195	1.0	< 0.001
Statins	1,180	5.8	1,258	6.2	0.103
ACEI/ARBs	1,960	9.6	1,965	9.7	0.932
Aspirin/clopidogrel	1,218	6.0	1,197	5.8	0.660
Warfarin	90	0.4	89	0.4	1

ACEI = angiotensin-converting enzyme inhibitor; ARBs = angiotensin II receptor-blockers; COPD = chronic obstructive pulmonary disease; PAOD = peripheral artery occlusive disease.

The P value for matched variables was not shown. Medications and five comorbidities (lung cancer, COPD, allergic rhinitis, asthma, and psoriasis) were not matched.

Table II. Predictors of ischemic stroke by Cox's proportional hazards regression analysis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Atopic dermatitis	1.29 (1.09–1.54)	0.003	1.33 (1.12–1.59)	0.001
Age ^a	1.09 (1.08–1.09)	< 0.001	1.07 (1.06–1.08)	< 0.001
Male sex	2.16 (1.82–2.56)	< 0.001	1.49 (1.25–1.78)	< 0.001
Comorbidities:				
Diabetes mellitus	4.22 (3.55–5.02)	< 0.001	1.34 (1.10–1.62)	0.003
Atrial fibrillation	7.04 (4.67–10.60)	< 0.001		
Hypertension	9.69 (7.98–11.75)	< 0.001	2.07 (1.63–2.63)	< 0.001
Coronary artery disease	6.26 (4.33–9.05)	< 0.001		
Valvular heart disease	2.79 (2.17–3.58)	< 0.001	1.37 (1.05–1.79)	0.020
PAOD	5.31 (2.37–11.87)	< 0.001		
Chronic kidney disease	3.32 (2.71–4.08)	< 0.001		
Dyslipidemia	3.38 (2.85–4.01)	< 0.001		
Lung cancer	4.31 (2.23–8.34)	< 0.001		
COPD	3.65 (3.07–4.34)	< 0.001		
Allergic rhinitis	0.90 (0.75–1.09)	0.278		
Asthma	2.34 (1.92–2.86)	< 0.001		
Psoriasis	1.65 (0.91–3.00)	0.099		
Medications:				
Statins	2.81 (2.23–3.55)	< 0.001		
ACEI/ARBs	4.62 (3.85–5.53)	< 0.001		
Aspirin/clopidogrel	5.72 (4.72–6.93)	< 0.001	1.34 (1.08–1.66)	0.007
Warfarin	5.29 (2.91–9.61)	< 0.001		

All factors with $P < 0.1$ in univariate analyses were included in the Cox's multivariate analysis.

ACEI = angiotensin-converting enzyme inhibitor; ARBs = angiotensin II receptor-blockers; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PAOD = peripheral artery occlusive disease.

^aHR for being 1 year older.

Table III. Risk factors for ischemic stroke, acute myocardial infarction (AMI), and heart failure (HF) in patients with atopic dermatitis and matched cohort.

Total CV events HR (95% CI)	P	Ischemic stroke HR (95% CI) ^a	P	AMI HR (95% CI) ^a	P	HF HR (95% CI) ^a	P
1.32 (1.15–1.52)	< 0.001	1.30 (1.08–1.56)	0.005	1.31 (0.88–1.95)	0.180	1.46 (1.10–1.93)	0.009

All HRs were adjusted for age, sex, comorbidities and medications listed in Table I. All factors with $P < 0.1$ in univariate analyses were included in the Cox's multivariate analysis.

Total CV events = the sum of ischemic stroke and AMI and HF.

^aAfter adjusting for competing risk

AMI = acute myocardial infarction; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.

valvular heart disease (HR, 1.37; 95% CI, 1.05–1.79; $P = 0.020$), and aspirin/clopidogrel (HR, 1.34; 95% CI, 1.08–1.66; $P = 0.007$; Table II).

After adjusting for patients' age, sex, comorbidities, medications, and competing risk, AD is also an independent risk factor for HF (HR, 1.46; 95% CI, 1.10–1.93; $P = 0.009$) and has a borderline increased risk for AMI (HR, 1.31; 95% CI, 0.88–1.95; $P = 0.180$; Table III). We identified that the dermatologist visits within one week, two weeks, one month, two months, or three months did not increase the risk of ischemic stroke occurrence (Table IV).

Predictors of ischemic stroke risk in patients with AD

Of the sample of 20,323 patients with AD, 17,328 (85.26%), 2,256 (11.10%), and 739 (3.64%) patients were assigned to the mild, moderate, and severe AD groups, respectively. Among all patients with AD, 301 (1.48%) had ischemic strokes during the follow-up period, including 215 (1.24%) patients in the mild AD group, 59 (2.62%) in the moderate group, and 27 (3.65%) patients in the severe group ($P < 0.001$).

The adjusted HRs for the risk of ischemic stroke in patients with mild, moderate, and severe AD were 1.20 (95% CI, 1.00–1.45; $P = 0.052$), 1.64 (95% CI, 1.23–2.19; $P = 0.001$), and 1.71 (95% CI, 1.15–2.56; $P = 0.008$). The log-rank test showed a higher cumulative incidence of ischemic stroke in the severe AD group than in the moderate and mild AD groups during the follow-up period ($P < 0.001$; Figure 2), indicating that patients with severe AD had an increased risk of ischemic stroke in the long term. Additionally, independent risk factors of ischemic stroke for patients with AD are shown in the Supplementary Table I to be found online at <http://informahealthcare.com/doi/abs/10.3109/07853890.2013.870018>.

Discussion

In this study, we demonstrated that AD is an independent risk factor for ischemic stroke. Patients with AD had a 33% increased incidence of ischemic stroke compared with the comparison group. We also demonstrated an 'exposure-response relationship', in that the patients with severe AD had a higher risk of ischemic

stroke than did those with less severe forms of the condition. These findings support the concept that AD may exert a systemic effect contributing to ischemic stroke.

To our knowledge, this is the largest population-based cohort study to investigate the risk of ischemic stroke among patients with AD. To avoid any confounding effect of pre-existing cerebrovascular disease, patients with a history of any type of stroke before the diagnosis of AD were excluded from this study. By including only first-time cerebrovascular events occurring after the diagnosis of AD, this study addressed the temporal relationship between AD and ischemic stroke. The results showed that patients with AD were prone to develop ischemic stroke independent of other major risk factors for a cerebrovascular event, including age, sex, and selected comorbidities.

Increasing evidence has shown that systemic inflammation can promote the progression of atherosclerosis and thrombosis to ischemic stroke (11,12). Possible explanations for the high risk of ischemic stroke in patients with AD are atherosclerotic changes (13–18) and activation of the coagulation system (6,19–27) related to chronic inflammation. Several observational studies have found that atherosclerotic changes in cardiovascular diseases may be associated with inflammatory processes resulting from autoimmune disorders, such as rheumatoid arthritis (13) and systemic lupus erythematosus (14); or from atopic diseases, such as asthma (15–18). Several studies have found associations between elevated platelet activation and chronic allergic diseases such as asthma (19,21) or psoriasis (6,24–27). Inasmuch as AD is also an allergic disease, albeit thought to be milder in severity as compared with asthma or psoriasis, it probably exerts systemic inflammatory effect in a similar fashion, thereby contributing to cardiovascular or cerebrovascular consequences. In this study, other atopic diseases

Table IV. Association of the risk of developing ischemic stroke with dermatologist visits.

	Univariate analysis		Multivariate analysis ^a	
	HR (95% CI)	P	HR (95% CI)	P
Dermatologist visits				
Last 3 months	1.07 (1.00–1.14)	0.059	1.01 (0.94–1.08)	0.799
Last 2 months	1.13 (1.03–1.23)	0.009	1.04 (0.95–1.14)	0.381
Last 1 month	1.28 (1.12–1.47)	< 0.001	1.12 (0.98–1.28)	0.088
Last 2 weeks	1.44 (1.11–1.88)	0.006	1.19 (0.93–1.54)	0.170
Last 1 week	1.72 (1.14–2.61)	0.010	1.29 (0.87–1.93)	0.211

^aAdjusted for age, sex, comorbidities, and medications listed in Table I.

CI = confidence interval; HR = hazard ratio.

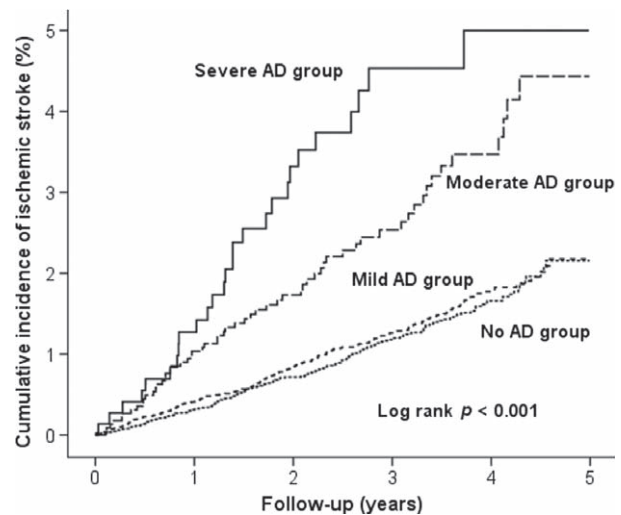


Figure 2. Cumulative incidence of ischemic stroke in patients with mild, moderate, severe, and no atopic dermatitis (AD) group.

including allergic rhinitis and asthma are not independent risk factors for ischemic stroke. The possible explanation is that non-atopic asthma is more common than atopic asthma among elderly patients. Allergic rhinitis seems to be milder and less systemic inflammation than other atopic diseases. However, there are few studies addressing the relationship of AD and cardiovascular disease. Tamagawa-Mineoka et al. (6) observed significantly elevated platelet activation in patients with AD by monitoring platelet activation markers such as β -thromboglobulin and platelet factor 4, levels of which were significantly higher in patients with AD than in comparisons, and which were significantly reduced after treatment in patients with AD and psoriasis. Plasma levels of platelet-derived microparticles and soluble P-selectin as platelet activation markers were significantly higher in AD patients compared with controls and reduced following skin lesion improvement by drug treatment (7). The two studies highlighted the phenomenon of platelet activation among patients with AD. One case-control study (8) conducted by Nastalek et al. selected 130 AD patients and 130 healthy controls. Fibrin clot function was assessed, and patients with AD had lower clot permeability, increased fiber thickness, faster clot formation, higher maximum D-dimer levels released from clots, and prolonged fibrinolysis time compared with controls. Nastalek et al. concluded that patients with AD were associated with formation of dense fibrin clots resistant to lysis.

Our findings suggest that AD is an independent risk factor for ischemic stroke. Elevated platelet activation and reduced efficiency of fibrinolysis can partly explain the relationship between AD and the increased risk of ischemic stroke. Because inflammatory parameters (e.g. C-reactive protein, erythrocyte sedimentation rate, procalcitonin) were unavailable in this study, the role of inflammation and the relationship between AD and ischemic stroke are not clear. Further research is needed to confirm our results and to determine the underlying pathogenesis. In order to get better quality of log-rank test, we completely matched age, sex, and comorbidities in the comparison group. Although age, sex, and comorbidities in the comparison group have been completely matched, overmatching bias is not excluded. We performed Cox's proportional hazards models to double-check. The result of log-rank test ($P = 0.003$; Figure 1) is very close to the result of Cox's proportional hazards models ($P = 0.001$; Table II).

There may be a surveillance bias in that those patients with AD are more likely to have frequent check-ups, which may lead to early detection of ischemic stroke. To avoid the surveillance bias, we use dermatologist visits as a variable, and the result indicated that the dermatologist visit is not a risk factor for ischemic stroke (Table IV). However, because the clinical evidence linking AD to ischemic stroke in clinical practice has been lacking, patients with AD are usually followed up by their dermatologists. Patients visit a neurologist or emergency specialist only when they have neurological symptoms, and then they undergo brain computed tomography/magnetic resonance imaging studies to diagnose ischemic stroke.

In this study, we found that some traditional risk factors for stroke, including atrial fibrillation and coronary artery disease and peripheral artery occlusive disease, seem very sensitive to change from the univariate to multivariate models (Table II). This may be due to the low prevalence of those traditional risk factors for ischemic stroke in the AD group. In this study, the incidence of psoriasis was significantly higher in patients with AD than in comparisons (1.7% versus 1.0%; $P < 0.001$). This is unusual because psoriasis and AD are clinically mutually exclusive (28). The increased psoriasis incidence in patients with AD may

be due to a surveillance bias. Patients with AD were more likely to have frequent dermatologist visits, which may lead to early detection of psoriasis. A growing body of evidence (29,30) has shown that psoriasis confers a higher risk for cardiovascular diseases. After multivariate adjustment, psoriasis was not an independent risk factor for ischemic stroke. This may be due to the very low prevalence of psoriasis in this study. More research is needed to clarify the role of psoriasis in the relationship of AD and stroke.

One particular strength of the present study is its nationwide, population-based study design, which could trace all cases of newly diagnosed AD and ischemic stroke in Taiwan during the study period, since all dermatologic and neurological practices were covered in our insurance system. Additionally, the large sample size, in our study, afforded substantial statistical power for detecting real, even subtle, differences between the two cohorts.

Our study has several limitations. First, patients with AD were identified using a diagnostic code in a database, introducing the possibility of misclassification because of coding errors or misdiagnosis. Second, some potential risk factors, including obesity, smoking, alcohol use, and family history of cardiovascular disease, were not included in our analyses because these data were not available. Nonetheless, some cigarette-smoking related health consequences would, at least in part, be reflected in the presentation of comorbidities, such as lung cancer or chronic obstructive pulmonary disease, which were covered in our analysis. Third, the follow-up period may not have been sufficiently long to detect ischemic stroke development. Fourth, we could not directly evaluate the severity of each comorbidity. Although the rate of each comorbidity has no difference between AD and comparison groups, the severity of each comorbidity may be different. We used vascular protection medications to adjust the cardiovascular risk. Patients with higher cardiovascular risk were prescribed with more vascular protection medication. Furthermore, the severity of AD was classified by AD medication prescriptions given in clinic visits, which may not exactly conform to the guidelines. Finally, because we did not have the information of causes of death, stroke may be a cause of death but was not recorded as an end-point. Nonetheless, non-differential misclassification led to a bias toward the null that reduces the effect of AD.

Conclusions

This large population-based study demonstrated that patients with AD had an increased risk of ischemic stroke, and that the risk probably increased with AD severity. We suggest that events of ischemic stroke should be routinely reported in future AD study. Future studies on the possible pathogenic mechanisms between AD and ischemic stroke are necessary.

Acknowledgements

This study is supported in part by a grant from Taipei Veterans General Hospital (V101D-001-2). The study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

Vincent Yi-Fong Su and Tzeng-Ji Chen contributed equally to this manuscript. Vincent Yi-Fong Su, Tzeng-Ji Chen, and Chia-Jen Liu outlined the data analysis and wrote the manuscript.

Chiu-Mei Yeh, Kun-Ta Chou, Man-Hsin Hung, and Szu-Ying Chu conducted the data analyses. Kang-Cheng Su, Yu-Sheng Chang, and Elizabeth Ya-Hsuan Lin collected the data and established the database. All authors critically reviewed the manuscript and were involved in the interpretation of data.

Declaration of interest: All the authors declare that there is no potential conflict of interest.

References

- Redon J, Olsen MH, Cooper RS, Zurriaga O, Martinez-Beneito MA, Laurent S, et al. Stroke mortality and trends from 1990 to 2006 in 39 countries from Europe and central Asia: implications for control of high blood pressure. *Eur Heart J*. 2011;32:1424–31.
- Woodruff TM, Thundiyil J, Tang SC, Sobey CG, Taylor SM, Arumugam TV. Pathophysiology, treatment, and animal and cellular models of human ischemic stroke. *Mol Neurodegener*. 2011;6:11.
- Saito H. Much atopy about the skin: genome-wide molecular analysis of atopic eczema. *Int Arch Allergy Immunol*. 2005;137:319–25.
- Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? *J Allergy Clin Immunol*. 2008;121:947–54 e915.
- Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from isaac phase three. *J Allergy Clin Immunol*. 2009;124:1251–8 e1223.
- Tamagawa-Mineoka R, Katoh N, Ueda E, Masuda K, Kishimoto S. Elevated platelet activation in patients with atopic dermatitis and psoriasis: increased plasma levels of beta-thromboglobulin and platelet factor 4. *Allergol Int*. 2008;57:391–6.
- Tamagawa-Mineoka R, Katoh N, Ueda E, Masuda K, Kishimoto S. Platelet-derived microparticles and soluble P-selectin as platelet activation markers in patients with atopic dermatitis. *Clin Immunol*. 2009;131:495–500.
- Nastalek M, Wojas-Pelc A, Undas A. Plasma fibrin clot properties in atopic dermatitis: links between thrombosis and atopy. *J Thromb Thrombolysis*. 2010;30:121–6.
- Universal Health Coverage in Taiwan. Taiwan National Health Insurance Administration Ministry of Health and Welfare. Available from: http://www.nhi.gov.tw/Resource/webdata/21717_1_20120808UniversalHealthCoverage.pdf (accessed May 2012).
- Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol*. 1992;135:1019–28.
- Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115–26.
- Elkind MS. Inflammatory markers and stroke. *Curr Cardiol Rep*. 2009;11:12–20.
- Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis*. 2006;65:1608–12.
- Bruce IN. 'Not only .. but also': factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2005;44:1492–502.
- Toren K, Lindholm NB. Do patients with severe asthma run an increased risk from ischaemic heart disease? *Int J Epidemiol*. 1996;25:617–20.
- Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, et al. Asthma and incident cardiovascular disease: The Atherosclerosis Risk in Communities study. *Thorax*. 2005;60:633–8.
- Onufrak S, Abramson J, Vaccarino V. Adult-onset asthma is associated with increased carotid atherosclerosis among women in the Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis*. 2007;195:129–37.
- Onufrak SJ, Abramson JL, Austin HD, Holguin F, McClellan WM, Vaccarino LV. Relation of adult-onset asthma to coronary heart disease and stroke. *Am J Cardiol*. 2008;101:1247–52.
- Lupinetti MD, Sheller JR, Catella F, Fitzgerald GA. Thromboxane biosynthesis in allergen-induced bronchospasm. Evidence for platelet activation. *Am Rev Respir Dis*. 1989;140:932–5.
- Pitchford SC, Yano H, Lever R, Rizzo-Vasquez Y, Ciferri S, Rose MJ, et al. Platelets are essential for leukocyte recruitment in allergic inflammation. *J Allergy Clin Immunol*. 2003;112:109–18.
- Averill FJ, Hubbard WC, Proud D, Gleich GJ, Liu MC. Platelet activation in the lung after antigen challenge in a model of allergic asthma. *Am Rev Respir Dis*. 1992;145:571–6.
- Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. *J Clin Invest*. 2005;115:3378–84.
- Ludwig RJ, Schultz JE, Boehncke WH, Podda M, Tandl C, Krombach F, et al. Activated, not resting, platelets increase leukocyte rolling in murine skin utilizing a distinct set of adhesion molecules. *J Invest Dermatol*. 2004;122:830–6.
- Hayashi S, Shimizu I, Miyauchi H, Watanabe S. Increased platelet aggregation in psoriasis. *Acta Derm Venereol*. 1985;65:258–62.
- Berrettini M, Parise P, Constantini V, Grasselli S, Nenci GG. Platelet activation in psoriasis. *Thromb Haemost*. 1985;53:195–7.
- Vila L, Sola J, Puig L, de Castellarnau C, de Moragas JM. Exogenous arachidonic acid metabolism in platelets from psoriatic patients. *Acta Derm Venereol*. 1990;70:110–14.
- Vila L, Cullare C, Sola J, Puig L, de Castellarnau C, de Moragas JM. Cyclooxygenase activity is increased in platelets from psoriatic patients. *J Invest Dermatol*. 1991;97:922–6.
- Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol*. 1995;32:982–6.
- Chiang CH, Huang CC, Chan WL, Huang PH, Chen YC, Chen TJ, et al. Psoriasis and increased risk of ischemic stroke in Taiwan: a nationwide study. *J Dermatol*. 2012;39:279–81.
- Tablazon IL, Al-Dabagh A, Davis SA, Feldman SR. Risk of cardiovascular disorders in psoriasis patients: current and future. *Am J Clin Dermatol*. 2013;14:1–7.

Supplementary material available online

Supplementary Table I.

Supplementary Table I. Predictors of ischemic stroke in patients with atopic dermatitis by cox proportional hazards regression analysis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age $\geq$ 40 years	25.73 (14.09–46.99)	< 0.001	10.67 (5.72–19.90)	< 0.001
Male sex	2.25 (1.79–2.83)	< 0.001	1.76 (1.40–2.22)	< 0.001
Diabetes mellitus	4.01 (3.18–5.05)	< 0.001	1.37 (1.08–1.75)	0.010
Atrial fibrillation	6.82 (3.91–11.89)	< 0.001	1.83 (1.03–3.24)	0.039
Hypertension	10.09 (7.79–13.05)	< 0.001	4.02 (3.04–5.31)	< 0.001
Coronary artery disease	7.12 (4.48–11.33)	< 0.001	1.80 (1.12–2.90)	0.016
Valvular heart disease	2.96 (2.13–4.09)	< 0.001	1.64 (1.17–2.30)	0.004
PAOD	6.34 (2.36–17.02)	< 0.001		
Chronic kidney disease	3.15 (2.39–4.15)	< 0.001		
Dyslipidemia	3.20 (2.55–4.01)	< 0.001		

Abbreviation: HR = hazard ratio; CI = confidence interval; PAOD = Peripheral artery occlusive disease. All factors with $p < 0.1$ in univariate analyses were included in the Cox multivariate analysis.